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### Research into neuropsychological assessment and cognitive rehabilitation in brain tumor patients after surgery

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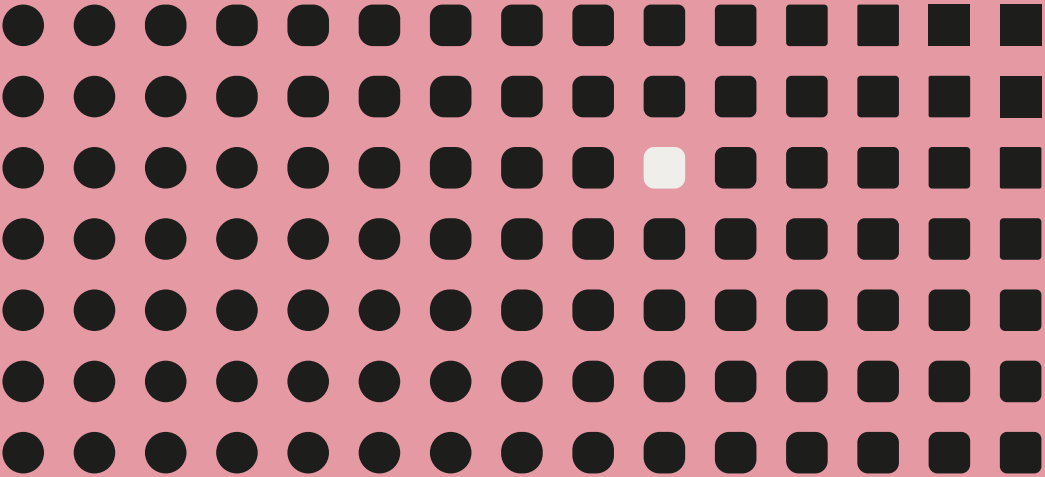
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Research into  
neuropsychological  
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Sophie Dorothee van der Linden

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Research into neuropsychological assessment and cognitive  
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**Proefschrift**

ter verkrijging van de graad van doctor aan Tilburg University op gezag van de rector  
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## CHAPTER 1

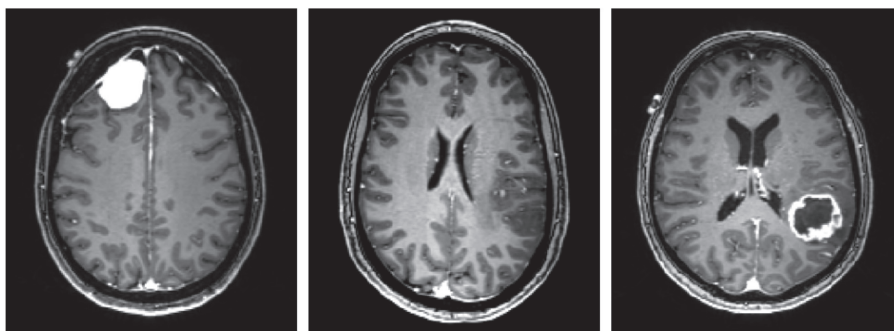
# General introduction and outline of the dissertation



In this dissertation, neuropsychological assessment and cognitive rehabilitation were investigated in patients with low-grade glioma and meningioma after neurosurgery, with the overarching goal to improve surgical aftercare for these patients.

## CENTRAL NERVOUS SYSTEM TUMORS

Primary central nervous system (CNS) tumors are a heterogeneous group of tumors that arise from cells and structures belonging to the CNS. Meningioma are the most common type and account for approximately 37% of all primary CNS tumors.<sup>1</sup> Meningioma originate from the arachnoidal cells of the meninges of the brain, and not from brain tissue itself (Figure 1a). They occur twice as often in women than in men and are most likely to be diagnosed in adults older than 60 years of age.<sup>1,2</sup> In the Netherlands, approximately 450 to 500 people are diagnosed with a symptomatic intracranial meningioma each year.<sup>3</sup> The far majority of meningioma are benign tumors (>90% WHO-grade I). These tumors are slow-growing, and patients generally have a favorable long-time prognosis. A distinct worse prognosis is observed in patients with atypical (WHO-grade II) or anaplastic (WHO-grade III) meningiomas, which account for approximately 5-7% and 1-2% of all meningiomas, respectively.<sup>3</sup> These tumors grow faster, more often invade the brain and are more likely to recur after treatment.<sup>2</sup> Observation (wait-and-scan), neurosurgical resection, radiosurgery and/or radiotherapy are the most common approaches in the management of meningioma.<sup>2,3</sup>



**Figure 1.** Patient with a a) Meningioma; b) Low-grade glioma; c) High-grade glioma

Glioma are tumors that grow from glial cells.<sup>1</sup> In the Netherlands, 1100 patients are diagnosed with a glioma every year<sup>4</sup>, mostly between the age of 45 and 65. Different types of gliomas can be distinguished, based on the type of glia cell from which they originate, for example astrocytoma and oligodendroglioma. Glioma can be classified according to histological and molecular features, as described in the classification system of the World

Health Organization.<sup>5</sup> Low-grade glioma are slow-growing tumors with more favorable characteristics, compared to high-grade glioma, which are more rapidly growing tumors (Figure 1b, c). Prognosis ranges widely, depending on tumor classification and the effects of treatment. The median survival of patients suffering from glioma ranges from 15 months for glioblastoma (the most frequent and malignant glioma) to 15 years for low-grade glioma with favorable molecular markers.<sup>6-8</sup> Multiple clinical and biological parameters (e.g., tumor location, tumor type, tumor size, WHO-grade, molecular markers, age of the patient, neurological functioning, general health status) determine the line of treatment. Generally, neurosurgery is the first choice of treatment, followed by radiotherapy and/or chemotherapy.

## COGNITIVE FUNCTIONING IN PATIENTS WITH BRAIN TUMORS

There is a large body of evidence indicating that a significant proportion of patients with brain tumors experience cognitive deficits, with prevalence estimates varying between 19% and 90%.<sup>9-11</sup> Cognitive deficits are often mild to moderate and most commonly observed in processing speed, attention, memory and executive functioning.<sup>9,11,12</sup> Cognitive functioning can be influenced by tumor characteristics (e.g., localization, type, or recurrence), and its treatment (neurosurgery, radiotherapy and/or chemotherapy).<sup>13</sup> Furthermore, epilepsy, symptoms of (mental) fatigue, sleep-wake disturbances and psychological distress are also present in a large number of patients with brain tumors and may affect cognitive functioning as well.<sup>14,15</sup> Cognitive problems, even if they are mild, can lead to problems in patients' daily life, including restrictions in social participation and work ability.<sup>16,17</sup> Moreover, they can lead to reductions in quality of life of patients with brain tumors.<sup>18,19</sup>

## ASSESSMENT OF COGNITIVE FUNCTION

Previously, most outcome measures in neuro-oncological studies, especially in the older studies, have been related to overall survival and progression-free survival. However, nowadays there has been consensus among the majority of researchers and clinicians that, in addition to medical outcome measures, neuropsychological outcome measures are also important to monitor during the disease process. Routine assessment of cognitive function may facilitate medical decision-making and can help to guide referral to appropriate care.<sup>20</sup> In line with this, the current national guidelines also stress the importance of routine monitoring of cognitive and psychological status.<sup>4</sup> Yet, routine assessment is not always embedded in standard clinical care in neurosurgical/neuro-oncological centers. Potential barriers to the implementation of routine assessment exist, including limited recourses in time, personnel and money.<sup>14,21</sup>

Computerized test batteries may facilitate the implementation of routine neuropsychological assessment into clinical practice and are increasingly being explored in the field of neuro-oncology.<sup>22-25</sup> At the department of neurosurgery of the Elisabeth-TweeSteden Hospital (ETZ), computerized neuropsychological assessments have, in collaboration with the department of Cognitive Neuropsychology of Tilburg University (TiU), been embedded in standard clinical care for patients who undergo a craniotomy since November 2010. Neuropsychological assessments are administered one day before surgery and three months after surgery and information from these assessments is also used in the multidisciplinary consultation that takes place every month. For research purposes, follow-up assessments one year and two years after surgery were added to the existing protocol in 2015, to allow evaluation of cognitive outcome on the longer-term. Although computerized tests cannot fully replace the diagnostic work of a clinical neuropsychologist, they have some important advantages including standardized test administration, and accurate as well as less time-consuming scoring procedures. Furthermore, our group has also demonstrated sufficient sensitivity of the computerized test battery CNS VS in the detection of (mild) cognitive deficits and change in cognitive function in patients with brain tumors.<sup>25-27</sup>

In parallel with our patient studies, we further investigated (within a collaboration between TiU and ETZ) normative values and psychometric properties of the CNS VS in a sample of Dutch healthy controls<sup>28,29</sup>, in order to be able to draw accurate conclusions on both individual performances of patients and change in cognitive functioning over time. First, we compared the existing norms of the American population ( $n = 1069$ ) to performance of Dutch healthy controls ( $n = 158$ ). Also, the effects of sex, age and education on test performance were evaluated. Since significant differences were observed between the American norms and Dutch healthy controls, as well as significant influences of sex, age and education, we developed regression-based norms based on our Dutch healthy sample. Subsequently, we evaluated change in test performance over time in this sample. Test-retest reliability and practice effects of the CNS VS were evaluated, and formulae were established for the determination of individual reliable change in cognitive performance over time, taking into account imperfect test-retest reliability and practice effects.

## PATIENT REPORTED OUTCOME MEASURES

In addition to the measurement of performance-based outcomes of cognitive functioning, assessment of patients' own experience is equally important in the light of patient-centered care, in order to get a complete picture of patients' everyday functioning. Patient reported outcome measures (PROMs) are defined as outcomes directly reported by patients (using self-report or interviews), which reflect the patient's perception of a disease and treatment.<sup>30</sup>

PROMs are useful to quantify symptoms, functioning, health-related quality of life or treatment satisfaction.<sup>30</sup> A distinction can be made between generic or condition-specific instruments.<sup>31</sup> The Cognitive Failures Questionnaire (CFQ<sup>32</sup>) is an example of a generic instrument, whereas the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT<sup>33</sup>) and the EORTC brain cancer-specific Quality of Life Questionnaire<sup>34</sup> are condition-specific instruments for patients with brain tumors. Several validated questionnaires can be used to assess the wide variety of possible complaints brain tumor patients can experience, including cognitive symptoms, psychological distress and fatigue. To be able to provide appropriate care, proper assessment of these symptoms is an important first step. However, filling out multiple lengthy questionnaires can be burdensome for neuro-oncological patients. Thus, the inclusion of PROMs is important in both research and clinical settings, but patient burden should be taken into account, by assessing as efficiently as possible.

In this thesis, particular attention is paid to the assessment of fatigue. Fatigue can be described as a subjective feeling of tiredness and a lack of energy, and therefore self-report questionnaires are probably the most suitable method to measure levels of fatigue. In oncological and neurological patients, fatigue is a very common symptom, but unfortunately often underdiagnosed and undertreated.<sup>35,36</sup> Research showed that fatigue in brain tumor patients is associated with cognitive complaints, depressive symptoms and sleep-wake disturbances, and moreover, that it affects patients' daily activities and quality of life.<sup>14,37,38</sup> More research is necessary to increase knowledge on the prevalence, severity and multifactorial determinants of fatigue in patients with meningioma and glioma.

## COGNITIVE REHABILITATION IN PATIENTS WITH BRAIN TUMORS

Although cognitive functioning of brain tumor patients is extensively investigated over the past decades, research on treatment options for cognitive deficits in this patient group is lagging behind. This is in contrast with research in other neurological patient populations, for example mild cognitive impairment and multiple sclerosis<sup>39-41</sup>, where much more research is being done on treatment of cognitive deficits, possibly because these disorders are more common or because brain tumor patients are not seen as potential candidates because of their generally poorer prognosis. However, we feel that more attention should be paid to the treatment of cognitive deficits. First and foremost, because cognitive deficits often disrupt the normal life of patients and lead to lowered quality of life.<sup>18,19</sup> Furthermore, due to improvements in medical treatment followed by increased life expectancy<sup>6,42</sup>, brain tumor patients live longer with various possible complaints, including cognitive deficits. Therefore, treatment of cognitive deficits, and also management of symptoms of fatigue and psychological distress, has become increasingly important in the management of the

disease.<sup>43</sup> Also, from research we know that patients and partners are in need of more support for these complaints, but that these needs are regularly unmet.<sup>44</sup>

Cognitive rehabilitation is one of the main treatment options for cognitive deficits. The goal of cognitive rehabilitation is helping patients to improve cognitive functioning or to compensate for their cognitive deficits. In cognitive rehabilitation, two methods can be distinguished, namely cognitive retraining and compensation training. Cognitive retraining aims to ameliorate affected cognitive functions by extensive practice over time. Over the past few years, meta-analyses demonstrated that patients can improve on the trained task, but evidence for long-lasting effects is often lacking and moreover, that effects in near to far transfer to other tasks appear to be small to non-existent.<sup>45</sup> Compensatory methods include strategy training, that help patients better cope with cognitive problems. Examples of strategy training are Goal Management Training<sup>46,47</sup> or learning to use external memory aids (including assistive devices).<sup>48</sup> A large body of evidence on the effectiveness of compensation training exists in different patient populations.<sup>48-50</sup>

A few studies have been conducted on the effects of cognitive rehabilitation in brain tumor patients, of which most studies demonstrated positive effects.<sup>47,51-55</sup> In the majority of studies, use was made of compensation methods, in some cases combined with retraining elements. However, there are still many questions left in this field. There is an ongoing debate about what timing would be most appropriate for cognitive rehabilitation, and what the target group should be. Early intervention ensures that patients and partners are well-informed and that they know how to handle cognitive problems timely. When cognitive function deteriorates, due to for example adjuvant treatment or disease progression, patients and their partners are better prepared and potentially, more resilient. On the other hand, early interventions can be burdensome and may not have high enough priority for patients immediately after surgery or adjuvant treatment. However, studies indicate that the need for supportive care is very high, especially in the early stage of the disease.<sup>44</sup> Regarding the target population for cognitive rehabilitation, patients can be preselected based on cognitive complaints (using questionnaires) or cognitive deficits (using neuropsychological tests). Another option is rehabilitation to optimize functioning in an early phase regardless of disorders or complaints, to potentially minimize impairments in functioning at a later stage, making use of the capabilities that are still intact. It seems a plausible option, given that a very large proportion of brain tumor patients experience cognitive deficits at a certain point during the disease trajectory. This more proactive approach, as an alternative to an impairment-driven approach, is also known as 'prehabilitation'. Prehabilitation has received increased attention over the last years, in other patient populations, particularly regarding

exercise before surgery.<sup>56,57</sup> Besides timing and target population, the ideal duration, intensity and follow-up of cognitive rehabilitation programs also remains largely unknown.

Recapitulating, there are still many uncertainties whether and how cognitive rehabilitation can have beneficial effects for patients with brain tumors. For this project, we emphasized the importance of proper clinical embedding of the program, in order to minimize patient burden. Amongst others, the intervention starts three months after surgery, after completion of adjuvant radiotherapy, and appointments are linked to existing appointments within the surgical aftercare in the hospital. Also, we chose to adopt a preventive and inclusive approach, intervening early in disease process, while not preselecting patients based on cognitive complaints or disorders.

## THE OPPORTUNITIES OF EHEALTH: DEVELOPMENT OF THE IPAD INTERVENTION REMIND

Although face-to-face cognitive rehabilitation programs have proven to be effective in patients with brain tumors<sup>51,52</sup>, they are accompanied by significant limitations. Multiple face-to-face sessions with a professional are necessary, which are time-consuming, costly, and require frequent hospital visits from patients. These multiple visits can be burdensome and are associated with indirect costs (e.g. time of work or travel costs<sup>58</sup>). Also, multiple hospital visits are not always feasible for individual patients, due to, for example, inability to drive. To overcome some of the limitations of conventional cognitive rehabilitation programs, use can be made of eHealth. Efficient use of eHealth saves time and costs, and also, increases the accessibility of interventions to patients.

In 2009, the large randomized controlled trial of Gehring and colleagues demonstrated positive effects of a face-to-face cognitive rehabilitation program, which was specifically developed for brain tumor patients, on cognitive functioning and mental fatigue in 140 glioma patients. Delivery of the program was highly intensive, as with other face-to-face programs, and after completion of the study, the program was no longer available for patients. In a joint patient-researcher initiative, the face-to-face program was converted into an iPad-based program (both in Dutch and English) (Figure 2), with the aim of improving availability and dissemination of the program. During the development of the *ReMind*-app, optimum use was made of the technical possibilities the new environment offered. Similar to the original program<sup>59</sup>, *ReMind* consists of compensation training, including psychoeducation and teaching of compensatory skills, and attention retraining. The iPad-based program allows patients to follow in-home cognitive rehabilitation at their own pace.



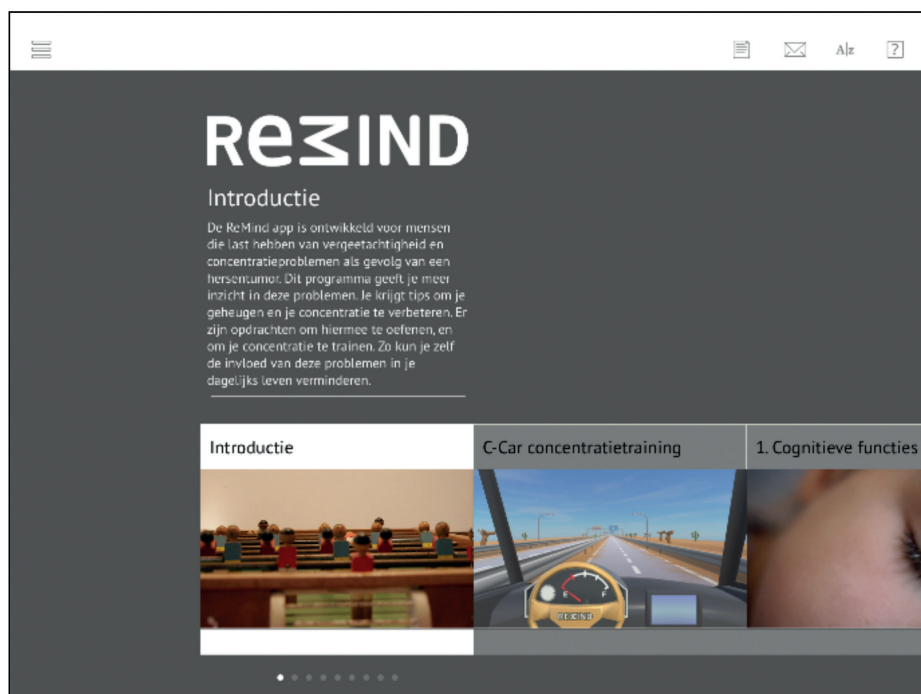


Figure 2. Homepage of ReMind

## INVOLVEMENT OF INFORMAL CAREGIVERS

As described before, brain tumor patients often suffer from cognitive deficits, mood disorders, severe fatigue or personality changes.<sup>14</sup> These symptoms, together with physical limitations, cause patients to depend increasingly on people in their environment for help and support.<sup>60</sup> At the same time, informal caregivers have to deal with these cognitive, emotional and behavioral symptoms, which leads to increased caregiver burden.<sup>61</sup> In the field of neuro-oncology, increased attention has been paid to experiences of informal caregivers over the last years, regarding functioning of the patient (e.g., symptom monitoring during different stages of the disease) and functioning of the caregivers themselves (e.g., caregiver burden<sup>62</sup>). Ultimately, involvement of informal caregivers may contribute to improved information exchange, better decision-making and treatment adherence, lower caregiver burden and higher self-efficacy of patients and caregivers. Thus, it is important to involve informal caregivers closely in the treatment of the patient and also, to provide informal caregiver support according to their needs.<sup>63,64</sup> In the research described in this thesis, informal caregivers were invited to participate in both symptom monitoring (i.e. executive functioning) and in the eHealth intervention.

## AIMS AND OUTLINE OF THIS DISSERTATION

In this thesis, we investigated assessment and rehabilitation of cognitive functioning and fatigue in patients with low-grade glioma and meningioma after neurosurgery, with the ultimate aim to improve the follow-up care for these patients. We have conducted different experimental studies, and in this thesis, data were used from a healthy control study, a cognitive rehabilitation study and a prospective longitudinal study on the prevalence, severity and prediction of cognitive outcome in brain tumor patients (the PREDICT-study).

In part I of the dissertation, neuropsychological assessment in patients with brain tumors receives attention. First, in a group of Dutch healthy controls, we investigated psychometric properties of the neuropsychological test battery CNS VS (**chapter 2**), which we used throughout all studies in this thesis. Test-retest reliability and practice effects of the CNS VS were evaluated, and formulae were proposed for the determination of individual reliable change in cognitive performance over time. In **chapter 3**, we focused on the assessment of executive functioning in patients with primary brain tumors, since deficits in executive functioning are among the most pronounced cognitive deficits in this patient group and have major impact on patients' daily functioning. Self-report of patients was compared with report of their informal caregivers (i.e. proxy-report or observer-report) on patients' EF and with performance-based measures of executive functioning. In **chapter 4**, we systematically examined the prevalence, severity and correlates of fatigue in patients with WHO-grade I meningioma. Fatigue is commonly reported by patients with meningioma in clinical care but has been scarcely studied in this patient group. Since patients with WHO-grade I meningioma have a relatively good long-term prognosis, follow-up care is quite limited and problems as cognitive deficits, fatigue and reduced quality of life can be overlooked in these patients with benign tumors.

In part II, we focus on post-surgical cognitive rehabilitation in brain tumor patients, evaluating the eHealth intervention *ReMind*. First, the results of a feasibility study on *ReMind* are presented in terms of accrual, attrition, adherence and patient satisfaction (**chapter 5**). After successful completion of the pilot study, we started a randomized controlled trial (RCT). The study protocol of the RCT on the efficacy of *ReMind* is described in detail in **chapter 6**. Subsequently, in **chapter 7**, we present the results of our RCT on the effects of *ReMind* on cognitive performance and PROs in patients with meningioma and low-grade glioma after neurosurgery. Finally, in **chapter 8**, the main findings of the dissertation are summarized, methodological considerations are discussed and implications for research and clinical practice are provided.

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PART I

# NEUROPSYCHOLOGICAL ASSESSMENT







## CHAPTER 2

# Test-retest reliability and practice effects of the computerized neuropsychological battery CNS Vital Signs: a solution-oriented approach



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## **ABSTRACT**

This study examined test-retest reliabilities and (predictors of) practice effects of the widely used computerized neuropsychological battery CNS Vital Signs. The sample consisted of 158 Dutch healthy adults. At 3- and 12-months follow-up, 131 and 77 participants were retested. Results revealed low to high test-retest reliability coefficients for CNS VS' test and domain scores. Participants scored significantly higher on the domains of Cognitive Flexibility, Processing Speed, and Reaction Time at the 3-month retest. No significant differences in performance were found over the second interval. Age, education, and retest-interval were not significantly associated with practice effects. These results highlight the need for methods that evaluate performance over time while accounting for imperfect test-retest reliabilities and practice effects. We provided RCI-formulae for determining reliable change, which may be a possible solution for future work facing the methodological issues of retesting.

## **PUBLIC SIGNIFICANCE STATEMENT**

Imperfect test-retest reliability and practice effects must be taken into account when interpreting change in neuropsychological test scores over time, for example by applying RCI-formulae for the determination of reliable change.

## INTRODUCTION

The use of repeated neuropsychological assessment, with the purpose of determining changes in cognitive functioning over time, is widespread in both clinical and research realms. A computerized neuropsychological test battery that is frequently used in serial assessment is Central Nervous System Vital Signs (CNS VS<sup>i</sup>). It has for example been used to evaluate the course of a disease (e.g.<sup>2-4</sup>), and to evaluate the effects of interventions (e.g.<sup>5-7</sup>).

Important considerations when interpreting performance on repeated neuropsychological assessments include imperfect test-retest reliabilities; that is random variability in scores which were gathered using the same instrument, in the same person, and under the same conditions<sup>8</sup>, and practice effects on follow-up testing performance (i.e., performance gain at retest due to familiarity with, and recognition of, test materials and procedures<sup>9,10</sup>). When the influence of these factors is ignored, erroneous conclusions can be drawn about the course of a disorder, for example by underestimating cognitive decline, or overestimating the effectiveness of a treatment. In general, changes in neuropsychological performance can be described in terms of raw change scores, reflecting the difference between a test and retest score without taking into account factors such as the test-retest reliability of an instrument or effects of practice. However, more suitable methods for determining whether observed changes within an individual represent real changes are available, such as reliable change indices (RCI).<sup>11,12</sup> Although many types of RCIs exist, all reflect a ratio of an estimate on an observed change score, as compared to change in a control group, and a corresponding standard error of measurement in the denominator.

CNS VS is suggested to be suitable for serial administration due to the generation of alternate forms through its random presentation of stimuli.<sup>1</sup> A few studies investigated the effects of retesting on CNS VS performance in the American population.<sup>1,13,14</sup> As CNS VS consists of seven tests that generate up to 11 cognitive domain scores, most studies use a selection of these domains. The test-retest reliability of CNS VS domain scores varied considerably per cognitive domain, where correlations ranged from .11 to .87, reflecting low to high test-retest reliability. Across the studies, results were largely consistent: low test-retest correlations were found for the domains of memory and adequate to high test-retest reliability was demonstrated for scores on measures of executive functioning, speed and reaction time.<sup>1,13,14</sup> Furthermore, Littleton, Register-Mihalik and Guskiewicz described that participants (N=40) performed better on 6 out of 9 cognitive domains on the second assessment compared to the first.<sup>14</sup> Consequently, it was concluded that practice effects do occur across serial testing sessions. No further changes were found between a second and third assessment.<sup>14</sup>

Although the former studies sought to determine CNS VS' psychometric properties in relation to repeated assessment, no firm conclusions can be drawn. Included sample sizes were small, rendering imprecise estimates of the test-retest correlations. Furthermore, the

literature describes several factors that are associated with differences in practice effects, such as age, education and test-retest interval.<sup>10</sup> However, the influence of education on practice effects of CNS VS has not yet been studied. Also, translated versions of CNS VS might be affected by cultural influences. Therefore, results from previous studies in American samples do not necessarily generalize to non-American samples.<sup>15</sup> More importantly, methods to deal with the previously demonstrated imperfect test-retest reliabilities and practice effects for use of CNS VS in daily (clinical) practice have not been provided.

The present study examines test-retest reliabilities and practice effects for the computerized neuropsychological battery CNS VS in a healthy Dutch sample, as well as factors that are known to be associated with practice effects (i.e., age, education, and time interval between assessments). Results will be placed into a solution-oriented perspective by the use of RCIs.

## METHODS

### Participants and Procedure

Participants were healthy Dutch adults recruited by convenience (i.e., from the broad network of the research group). They were considered healthy if 1) they had no major illnesses in the past year (e.g., cancer, myocardial infarction); 2) there was no past or present psychiatric or neurologic disorder; 3) they were free of any centrally acting psychotropic medication; and 4) did not have a history of drug abuse. All participants provided written informed consent and filled out a screening questionnaire querying their health status. Information regarding age, sex, educational level, and familiarity with computers was obtained by means of a checklist.

The CNS VS battery was administered at three times: at 'baseline' (T0), at 3-months (T3) and 12-months (T12). Participants were assessed individually following a standardized protocol at the university, hospital, or at the participant's home. All testing was done using the CNS VSX local software application, on the same type of laptop computers running Windows 7 Professional on 64-bit operating systems with background programs shut down and disconnected from Internet resources. Well-trained test technicians remained present during the entire assessment and ensured appropriate conditions. At retest, technicians checked for health issues or major life events since the previous assessment.

Baseline CNS VS performance of this study sample, including the effects of sociodemographic variables, was described in a previous publication.<sup>16</sup> The study was approved by the Medical Ethics Committee (file number NL41351.008.12).

### **CNS Vital Signs**

Cognitive functioning was assessed using the formal Dutch translation of the commercially available computerized neuropsychological test battery CNS VS (<http://www.cnsvs.com>). Its seven individual tests yield measures of performance in eleven cognitive domains. Stimuli are randomly presented over sessions. However, since 4 domains (i.e., composite memory, executive functioning, simple attention, and motor speed) generated by CNS VS show considerable overlap with other domains of the battery, only seven cognitive domains will be considered in this study, as well as 16 test scores (see Table 1). It takes approximately 30-40 minutes to complete the battery, after which automatic scoring facilitates the immediate availability of test results. Results are presented as raw scores, comprising of the number of correct and incorrect responses as well as mean reaction times in milliseconds.<sup>1</sup>

Table 1. Supplementary material on CNS Vital Signs

Cognitive domain	CNS VS test(s)	Domain score calculations ([Formulas for Calculating Domain Scores], n.d.)	Description
Verbal memory	Verbal memory test (VBM)	VBM direct correct hits + VBM direct correct passes + VBM delayed correct hits + VBM delayed correct passes	Learning a list of 15 words, with a direct recognition, and after 6 more tests a delayed recognition trial
Visual memory	Visual memory test (VIM)	VIM direct correct hits + VIM direct correct passes + VIM delayed correct hits + VIM delayed correct passes	Learning a list of 15 geometric figures, with a direct recognition, and after 6 more tests a delayed recognition trial
Processing speed	Symbol digit coding (SDC)	SDC correct responses – SDC errors	Number 1 to 9 correspond to different symbols. As many correct numbers as possible have to be filled out underneath the presented symbols in 90 seconds
Psychomotor speed	Finger tapping test (FTT) Symbol digit coding test (SDC)	FTT taps right hand + FTT taps left hand + SDC correct responses	Pressing the space bar with the index finger as many times in 10s Above-mentioned
Reaction time	Stroop test (ST)	(ST part II reaction time on correct responses + ST part III reaction time on correct responses) / 2	In part I, pressing the space bar as soon as the word RED, YELLOW, BLUE, and GREEN appear - in part II, pressing the space bar as the color of the word matches what the word says – in part III, pressing the space bar as the color of the word does not match what the word says
Complex attention	Continuous performance test (CPT) Shifting attention test (SAT) Stroop test (ST)	ST commission errors + SAT errors + CPT commission errors + CPT omission errors	Responding to a target stimulus 'B' but no any other letter Shifting from one instruction to another quickly and accurately (matching geometric objects either by shape or color) Above-mentioned
Cognitive flexibility	Shifting attention test (SAT) Stroop test (ST)	SAT correct – SAT errors – ST commission errors	Above-mentioned Above-mentioned

## Statistical analysis

*Participants' Characteristics.* Descriptive analyses of characteristics (i.e., age, sex, years of education, frequency of computer use, and baseline cognitive performance) of the participants who completed all three assessments, versus participants who dropped out after T0 or T3, were performed.

*Test-retest Reliability.* To examine the strength of the relationship between the test and retest scores, a series of Pearson product-moment correlations, or Spearman rho correlations in case of non-normally distributed data, were calculated for CNS VS' raw domain and test scores of T0 with those of T3, and for CNS VS' raw domain and test scores of T3 with those of T12. However, as Pearson's correlations only capture the linear association between scores, high values do not imply that the scores on pretest and posttest are identical. This means that Pearson's correlations are able to show to what extent the rank ordering of participants on the construct is stable over assessments, but they fail to show to what extent the same scores are obtained. Therefore, intra-class correlation coefficients (ICCs; see Schuck, 2004<sup>17</sup>) were calculated, which use a more stringent definition of reproducibility of scores. In particular, a distinction is made between ICCs for consistency ( $ICC_{con}$ ) and ICCs for agreement ( $ICC_{agr}$ ). ICCs for consistency evaluate to what extent scores at posttest differ from pretest by a constant. High ICCs for consistency are obtained when test scores are reliable, but all scores are elevated by the same amount (e.g., due to a constant practice effect). ICCs for agreement evaluate to what extent participants obtain exactly the same scores at the test and retest. High ICCs for agreement indicate that scores are stable and reproducible over time and rule out practice effects and instability of the construct envisaged. For the computations of the ICCs, a two-way mixed model was used and both ICCs of consistency and absolute agreement were evaluated at the level of single measures. Test-retest reliability coefficients of  $\geq .70$  were acceptable.<sup>18,19</sup> Additionally, the following categories were distinguished for further interpretation of reliability coefficients: coefficients  $< .60$  are considered low,  $.60-.69$  are marginal,  $.70-.79$  are adequate,  $.80-.89$  were considered high, and coefficients  $\geq .90$  are very high.<sup>19,20</sup>

*Practice Effects.* Paired-sample *t*-tests were performed to evaluate potential changes in participants' CNS VS' raw domain and test scores from T0 to T3, and from T3 to T12. To assess the magnitude of change, effect sizes (ES) were determined with Cohen's *d*.<sup>1</sup> ES between  $\leq .20$  -  $.49$  were considered as small,  $.50-.79$  as medium, and  $\geq .80$  as large sized effects.<sup>21</sup>

1  $M1 - M2 / \sqrt{SD1^2 + SD2^2}$ , with M1 and SD1 representing the mean and standard deviation of the test score, and M2 and SD2 representing the mean and the standard deviation of the retest score.



*Potential Predictors of Practice Effects.* If practice effects depend on background characteristics, the change in neuropsychological performance of participants is different across different levels of the background variables (e.g., change scores may be larger in younger participants compared to older participants). Therefore, to identify potential predictors of the magnitude of practice effects, a series of multiple linear regression analyses was conducted using raw CNS VS change scores as the outcome variables and a predetermined list of sociodemographic predictors. Age (in years), education (classified according to the Dutch Verhage scale<sup>22</sup>) ranging from unfinished primary school (1) to university level (7). Its seven categories were merged into three ordinal categories; low (Verhage 1 to 4), middle (Verhage 5), and high educational level (Verhage 6 and 7), which were dummy coded with middle education as reference category), and test interval (in weeks) were predictor variables which were entered as a single block ('enter' method). Assumptions were evaluated as follows: independence of observations was evaluated by Durbin-Watson tests (its values should be approximately 2<sup>23</sup>), and linearity and homoscedasticity were examined using scatter plots of residuals. Indications of potential multicollinearity between predictors was examined by inspecting Pearson's correlation coefficients and variance inflation indices, which should respectively not exceed 0.80 and 10.<sup>24</sup> By computing Cook's distances, which should be  $\leq 1$ , univariate influential cases were identified.<sup>5</sup> Normality of residuals was investigated by visual inspection of histograms.

*Reliable Change Indices.* In order to determine whether observed changes reliably reflect true changes in cognitive performance, whilst considering amongst others test-retest reliabilities and practice effects, the adjusted regression-based RCI ( $\text{adjRCI}_{\text{srb}}$ ) presented by Maassen, Bossema, and Brand<sup>26</sup> was employed in the current study as follows,

$$\text{AdjRCI}_{\text{srb}} = \frac{D_i - \bar{D}_c + [1 - (S_y/S_x)](x_i - \bar{x}_c)}{\sqrt{(S_x^2 + S_y^2)(1 - r_{xy})}} \quad (1)$$

The numerator in Equation 1 represents the estimated true change, and the denominator the corresponding standard error. Furthermore, variables  $D_i$  and  $\bar{D}_c$  denote to the observed difference between the raw test score and retest score for the individual  $i$  and the average difference score in a control group (our sample of healthy participants)  $c$ , respectively.  $S_x$  and  $S_y$  denote the standard deviation of the raw test scores  $x$  and retest scores  $y$  in the control group. Variable  $X_i$  represents the raw test score for the individual, and  $\bar{X}_c$  is the average raw score in the control group. Coefficient  $r_{xy}$  is the test-retest correlation, which here represents the test-retest reliability. For further details about this method, see formula (10) in Maassen, Bossema, and Brand.<sup>26</sup>

RCI formulae were established for each cognitive domain. Positive RCI values indicate that performance has improved at the retest assessment as compared to the preceding assessment, and vice versa for negative RCIs representing decline. RCIs are assumed to be

standard normally distributed under the null model of no change. This property allows to test whether change is statistically significant at the desired alpha level. In particular, for the alpha level of 0.10 (corresponding to a confidence interval of 90%), a statistically significant improvement or decline is observed when an RCI-value exceeds  $\pm 1.645$ . In those cases, one speaks of reliable change.

Data were analyzed using SPSS (Version 23.0; IBM SPSS Inc.). To reduce false discovery rate due to multiple testing, resulting *p*-values (i.e., from the descriptive analyses of characteristics, and analyses with regard to (predictors of) practice effects) were set against a corrected alpha, using the Benjamini-Hochberg (BH) procedure.<sup>27</sup>

## RESULTS

### Participants' Characteristics

Table 2 presents the sociodemographic characteristics of the participants. A total of 158 Dutch healthy participants were enrolled in the study and completed T0, of whom 131 participants also completed T3. As part of an earlier project, T0 and T3 assessments were already completed in 33 participants. No T12 assessment was performed in these participants. Nevertheless, the previously collected data were included in the database of the current study. Of the resulting 98 participants, 77 participants completed all three assessments. To sum up, 81 participants did not complete all assessments. Besides the expired follow-up time for 33 participants who were assessed as part of an earlier project, the most important reasons for discontinuation were difficulties in contacting the participants for follow-up assessment and that participants had busy schedules and other priorities. Nevertheless, between group comparisons revealed no significant baseline differences between participants who dropped out the study and those who did not, on age, years of education, sex, and baseline cognitive performance (*p*-values > BH-corrected alpha .004).

Mean age of the participants was 45.9 ( $\pm 14.4$ ) years at the time of baseline assessment. Fifty-seven percent of the sample was female; participants completed 16.9 ( $\pm 3.3$ ) years of education on average. The median time interval between T0 and the 3-month assessment T3 was 3.5 months (mean 4.2 $\pm$ 1.7 months), with a range of 2.0 – 9.2 months. Median time interval between the 3-month and 12-month interval (T3 and T12) was 8.3 months (mean 7.6 $\pm$ 2.0 months), with a range of 3.7 – 11.0 months.

**Table 2.** Characteristics of dropouts and groups who underwent baseline, 3- and 12-month follow-up assessment with CNS VS

	T0 (n = 158)	T3 (n = 131)	T12 (n = 77)	Drop-outs (n = 81)
Age at baseline (mean $\pm$ SD) (range)	45.94 $\pm$ 14.43 (20-80)	45.73 $\pm$ 14.54 (20-80)	46.62 $\pm$ 14.02 (20-80)	45.28 $\pm$ 14.87 (20-78)
Sex; male (n;%)	68; 43.0%	51; 38.9%	28; 36.4%	40; 45.3%
Years of education (mean $\pm$ SD) (range)	16.88 $\pm$ 3.30 (10-26)	16.77 $\pm$ 3.16 (10-24)	16.61 $\pm$ 3.39 (10-24)	17.14 $\pm$ 3.20 (10-26)
Level of education <sup>a</sup> (n; % <sup>b</sup> )				
Low	19; 12.0%	15; 11.5%	12; 15.6%	7; 8.6%
Middle	57; 36.1%	46; 35.1%	27; 35.1%	30; 37.0%
High	82; 51.9%	70; 53.4%	38; 49.4%	44; 54.3%
Computer use <sup>c</sup> (n;% <sup>b</sup> )				
Never	1; 0.6%	1; 0.8%	1; 1.3%	-
Some	4; 2.5%	4; 3.1%	4; 5.2%	-
Frequent	153; 96.8%	126; 96.2%	72; 93.5%	81; 100%

<sup>a</sup> Education is classified according to the Dutch coding system of Verhage<sup>22</sup> and categorized as follows: low educational level (Verhage 1 to 4), middle educational level (Verhage 5), and high educational level (Verhage 6 and 7).

<sup>b</sup> Percentages do not always sum up to 100 due to rounding

<sup>c</sup> Computer use was rated on a three-point scale with categories 'never', 'some', or 'frequent'.

### Test-retest Reliability

Table 3 lists detailed results of the test-retest reliability analyses, including Pearson/Spearman correlations and ICCs for consistency and agreement. ICCs for consistency of CNS VS' domain scores ranged from .40 to .89. For the individual tests scores, ICCs between .17 and .88 were found. Test-retest correlation coefficients of the second interval (T3-T12) generally appeared to be higher than the coefficients of the first interval (T0-T3). Overall, minor differences between Pearson/Spearman correlation coefficients and both ICCs for consistency and ICCs for agreement were observed.

Adequate to high reliability correlation coefficients were observed on the domains of Reaction Time, Cognitive Flexibility, Psychomotor Speed and Processing Speed as well as on the tests of Finger Tapping, Symbol Digit Coding and Shifting Attention. Reliability correlation coefficients of domains and tests of memory were low, suggesting poor reliability of test scores on these measures. Scores on the domain of Complex Attention showed poor test-retest reliability over the first interval (T0-T3), and turned out to be marginal, but still inadequate, over the second interval (T3-T12). Reliability correlation coefficients on the

Stroop Test were poor over the first interval (T0-T3). Over the second interval (T3-T12), ICCs of part II and III were adequate and high, but reliability correlation coefficients on part I remained inadequate. Due to minimal variance of (in-) correct responses on the Continuous Performance Test, the calculation of valid test-retest reliability correlation coefficients was not possible.

### Practice Effects

As shown in Table 4, a series of two-tailed paired-sample *t*-tests demonstrated statistically significant (given a BH-corrected alpha of .009) changes between mean group performances at T0 and T3 on 3 out of 7 raw cognitive domain scores: performance was improved on Reaction Time ( $t(127) = 3.84, p = <.001$ , Cognitive Flexibility ( $t(127) = -4.81, p <.001$ ), and Processing Speed ( $t(130) = -2.67, p = .0085$ ) at T3. No significant changes in mean scores were found for Verbal Memory, Visual Memory, Psychomotor Speed, and Complex Attention. Effect sizes were small, with Cohen's *ds* ranging from 0.15 to 0.32. There were no statistically significant changes in mean domain scores between T3 and T12 for any of the domains.

Inspection of the mean differences for the individual tests showed significantly higher raw scores on six out of seventeen measures at T3 compared to T0. Participants showed more correct responses in the direct recognition part of the Verbal Memory Test, and more correct answers on both the Symbol Digit Coding Test as well as the Shifting Attention Test at T3. Furthermore, faster responses were found for condition II and III of the Stroop Test, and the Shifting Attention Test. All effect sizes were small, with Cohen's *ds* ranging from 0.09 to 0.33. Again, no statistically significant changes were found on any of the tests between scores obtained between T3 and T12.

### Potential Predictors of Change

None of the assumptions regarding the regression analyses were violated. No significant effects (given a BH-corrected alpha of .004) of age, education, and duration of T0-T3 test interval were found on change in performance on any of the CNS VS' raw domain scores: Verbal Memory ( $F(4, 118) = 1.68, p = .159, R^2 = .054$ ), Visual Memory ( $F(4, 120) = 1.28, p = .282, R^2 = .041$ ), Psychomotor Speed ( $F(4, 125) = 1.21, p = .310, R^2 = .037$ ), Reaction Time ( $F(4, 123) = 0.75, p = .560, R^2 = .024$ ), Complex Attention ( $F(4, 121) = .79, p = .537, R^2 = .025$ ), Cognitive Flexibility ( $F(4, 123) = 1.31, p = .268, R^2 = .041$ ), Processing Speed ( $F(4, 126) = 0.94, p = .445, R^2 = .029$ ). Along the same lines, no significant effects of the predictors were found on change in CNS VS domain scores for the T3-T12 test interval: Verbal Memory ( $F(4, 69) = 1.68, p = .164, R^2 = .089$ ), Visual Memory ( $F(4, 69) = 2.69, p = .038, R^2 = .135$ ), Psychomotor Speed ( $F(4, 71) = 0.64, p = .635, R^2 = .035$ ), Reaction Time ( $F(4, 72) = 0.69, p = .599, R^2 = .037$ ), Complex Attention ( $F(4, 71) = 1.08, p = .374, R^2 = .057$ ), Cognitive

## Chapter 2

Flexibility ( $F(4, 71) = 1.59, p = .187, R^2 = .082$ ), and Processing Speed ( $F(4, 72) = 0.35, p = .847, R^2 = .019$ ).

Table 3. Test-retest reliabilities of CNSVS' raw domain and test scores within the Dutch sample

	Assessment T0 and T3 (n =131)				Assessment T3 and T12 (n =77)			
	r / ρ	ICC <sub>con</sub>	ICC 95% CI	ICC <sub>agr</sub>	ICC 95% CI	r / ρ	ICC <sub>con</sub>	ICC <sub>agr</sub>
<i>Cognitive domains</i>								
Verbal MemoryΔ	.43	.46	.31 - .59	.45	.30-.58	.50	.50	.50
Visual Memory	.41	.41	.25 - .55	.41	.25-.55	.41	.40	.41
Psychomotor Speed	.88	.87	.83 - .91	.87	.83-.91	.89	.89	.88
Reaction TimeΔ	.78	.74	.65 - .81	.72	.60-.80	.88	.88	.88
Complex AttentionΔ	.55	.56	.43 - .67	.55	.42-.66	.60	.69	.68
Cognitive FlexibilityΔ	.74	.72	.62 - .79	.68	.53-.78	.84	.81	.80
Processing Speed	.81	.80	.73 - .86	.79	.72-.85	.84	.84	.84
<i>Verbal Memory Test</i>								
Direct correct hitsΔ	.38	.34	.18 - .49	.33	.17-.47	.43	.40	.40
Direct correct rejectionsΔ	.18	.17	.00 - .33	.17	.00-.34	.28	.38	.37
Delayed correct hitsΔ	.46	.45	.30 - .58	.45	.30-.58	.47	.42	.42
Delayed correct rejectionsΔ	.30	.38	.21 - .52	.38	.21-.52	.47	.57	.56
<i>Visual Memory Test</i>								
Direct correct hits	.47	.47	.32 - .60	.47	.32-.59	.24	.24	.24
Direct correct rejections	.25	.25	.08 - .41	.25	.08-.41	.43	.43	.43
Delayed correct hits	.41	.41	.25 - .55	.41	.26-.55	.38	.37	.38
Delayed correct rejections	.35	.35	.18 - .49	.35	.18-.49	.59	.58	.59
<i>Finger Tapping Test</i>								
# taps right average	.82	.81	.74 - .86	.81	.74-.86	.76	.76	.76

Table 3. Continued

	Assessment T0 and T3 (n =131)					Assessment T3 and T12 (n =77)				
	r / $\rho$	ICC	ICC 95% CI	ICC <sub>agr</sub>	ICC	r / $\rho$	ICC	ICC 95% CI	ICC <sub>agr</sub>	ICC
# taps left average	<b>.87</b>	<b>.87</b>	.82 - .90	<b>.87</b>	<b>.87</b>	<b>.87</b>	<b>.87</b>	.80 - .91	<b>.87</b>	<b>.87</b>
<i>Symbol Digit Coding Test</i>										
# correct responses	<b>.85</b>	<b>.85</b>	.79 - .89	<b>.84</b>	<b>.84</b>	<b>.88</b>	<b>.88</b>	.82 - .92	<b>.88</b>	<b>.88</b>
<i>Stroop Test</i>										
Reaction time part I	.46	.46	.32 - .59	.46	.46	.68	.67	.52 - .78	.66	.66
Reaction time part II	.65	.65	.54 - .74	.63	.63	<b>.78</b>	<b>.77</b>	.67 - .85	<b>.78</b>	<b>.78</b>
Reaction time part III	.60	.60	.47 - .70	.58	.58	<b>.82</b>	<b>.81</b>	.72 - .88	<b>.81</b>	<b>.81</b>
<i>Shifting Attention Test</i>										
# correct responses	<b>.79</b>	<b>.78</b>	.71 - .84	<b>.74</b>	<b>.74</b>	<b>.85</b>	<b>.84</b>	.76 - .90	<b>.84</b>	<b>.84</b>
Reaction time	<b>.81</b>	<b>.80</b>	.73 - .86	<b>.78</b>	<b>.78</b>	<b>.86</b>	<b>.86</b>	.79 - .91	<b>.86</b>	<b>.86</b>

Note: r = Pearson product moment correlation coefficient,  $\rho$  = Spearman rho correlation coefficient, ICC = intraclass correlation coefficient, CI = confidence interval.  
Correlation coefficients of  $\geq .70$  were considered acceptable (in bold)  
 $\Delta$  Non-normally distributed, Spearman's rho was used

**Table 4.** Changes in performance on CNS Vital Signs' domain and test performance between T0-T3 and T3-T12

Domain	Assessment T0 and T3 (n =131)					Assessment T3 and T12 (n =73)				
	T0M (SD)	T3M (SD)	Mean diff. <sub>a</sub>	p*	Effect size <sub>b</sub>	T3M (SD)	T12M (SD)	Mean diff. <sub>a</sub>	p*	Effect size <sub>b</sub>
Verbal Memory	52.04 (4.37)	52.86 (4.55)	0.82	.052	0.18	52.59 (4.67)	52.11 (5.60)	-0.49	.422	-0.09
Visual Memory	46.27 (4.34)	46.06 (4.81)	-0.21	.641	-0.05	45.53 (4.73)	45.84 (5.31)	0.31	.628	0.06
Psychomotor Speed	179.05 (20.42)	180.05 (23.50)	0.99	.310	0.05	175.95 (22.08)	177.82 (22.47)	1.87	.131	0.08
Reaction Time <sub>c</sub>	632.06 (68.24)	615.30 (67.86)	16.77	<.001*	0.25	623.55 (79.62)	622.00 (80.96)	1.55	.731	0.02
Complex Attention <sub>c</sub>	6.44 (4.30)	5.68 (4.07)	0.76	.031	0.18	5.96 (3.63)	5.46 (4.25)	0.50	.168	0.13
Cognitive Flexibility	46.90 (11.37)	50.66 (12.14)	3.77	<.001*	0.32	49.39 (11.83)	51.13 (12.99)	1.74	.053	0.14
Processing Speed	57.66 (11.47)	59.47 (13.09)	1.81	.0085*	0.15	57.96 (13.28)	59.79 (13.16)	1.83	.032	0.14
<b>Test</b>										
Verbal Memory Test										
Direct correct hits	12.36 (2.08)	12.91 (1.66)	0.55	.005*	0.09	12.87 (1.68)	12.73 (1.95)	-0.13	.565	-0.07
Direct correct rejections	14.37 (0.82)	14.30 (1.04)	-0.07	.510	-0.08	14.16 (1.18)	13.99 (1.37)	-0.17	.296	-0.13
Delayed correct hits	11.03 (2.53)	11.50 (2.46)	0.46	.051	0.19	11.55 (2.38)	11.68 (2.79)	0.12	.709	0.05
Delayed correct rejections	14.23 (1.03)	14.14 (1.27)	-0.09	.445	-0.08	14.00 (1.43)	13.66 (1.53)	-0.34	.037	-0.23
Visual Memory Test										
Direct correct hits	11.90 (1.84)	11.66 (1.88)	-0.23	.168	-0.13	11.61 (1.79)	11.61 (1.82)	0.00	1.00	0.00
Direct correct rejections	11.80 (1.89)	11.94 (2.05)	0.14	.511	0.07	11.85 (1.87)	12.04 (1.98)	0.19	.435	0.10
Delayed correct hits	10.81 (1.87)	10.78 (2.07)	-0.02	.900	-0.02	10.73 (2.02)	10.84 (2.17)	0.11	.695	0.05



Table 4. Continued

	Assessment T0 and T3 (n =131)				Assessment T3 and T12 (n =73)					
	T0 M (SD)	T3 M (SD)	Mean diff. <sub>a</sub>	p*	Effect size <sub>b</sub>	T3 M (SD)	T12 M (SD)	Mean diff. <sub>a</sub>	p*	Effect size <sub>b</sub>
Delayed correct rejections	11.77 (1.92)	11.63 (2.15)	-0.14	.516	-0.07	11.36 (2.26)	11.31 (2.47)	-0.05	.831	-0.02
Finger Tapping Test										
# taps right average	62.05 (7.34)	61.45 (8.51)	-0.60	.165	-0.08	60.19 (7.95)	60.08 (7.89)	-0.11	.857	0.01
# taps left average	58.26 (7.23)	57.88 (7.85)	-0.37	.278	-0.05	56.74 (6.87)	56.88 (7.30)	-0.14	.745	0.02
Symbol Digit Coding Test										
# correct responses	58.98 (11.65)	60.86 (12.83)	1.89	.002*	0.15	59.31 (13.02)	60.78 (12.99)	1.47	.046	0.11
Stroop Test										
Reaction time part I <sub>c</sub>	276.75 (46.03)	278.41 (44.11)	-1.67	.686	0.04	278.62 (46.83)	285.76 (54.44)	-7.15	.137	-0.14
Reaction time part II <sub>c</sub>	585.65 (72.98)	570.05 (72.48)	15.59	.004*	0.21	573.05 (77.58)	572.94 (65.75)	0.12	.983	0.00
Reaction time part III <sub>c</sub>	678.72 (84.90)	656.38 (98.86)	22.34	.003*	0.24	673.44 (93.03)	670.60 (110.14)	2.84	.693	0.03
Shifting Attention Test										
# correct responses	53.13 (8.05)	55.98 (9.33)	2.86	<.001*	0.33	54.80 (9.17)	56.03 (9.93)	1.22	.049	0.13
Reaction time <sub>c</sub>	1075.33 (170.54)	1032.46 (186.24)	42.88	<.001*	0.24	1061.16 (188.09)	1041.78 (195.48)	19.38	.101	0.10
Continuous Performance Test										
# correct responses	39.94 (0.27)	39.83 (0.95)	-0.11	.214	-0.16	39.91 (0.40)	39.87 (0.73)	-0.04	.689	-0.07

**Table 4.** Continued

\* Statistical significance was considered as  $p < .009$ . Alpha was adjusted using the Benjamini-Hochberg procedure.<sup>27</sup>

<sup>a</sup> positive mean differences represent improvements

<sup>b</sup> Cohen's  $d$  effect sizes:  $\leq 0.20$  – 0.49: small, 0.50 – 0.79: medium,  $\geq 0.80$ : large.<sup>21</sup>

<sup>c</sup> higher scores indicate lower performance

## Reliable Change Indices

Table 5 shows RCI formulae for the determination of reliable change in CNS VS' domain scores over repeated assessments of the T0-T3 interval. Since practice effects were only observed between the first and second assessment, RCI-formulae for the determination of change over the second time interval are not described but available upon request. An example of the use of RCI formulae is presented in Box 1.

**Table 5.** RCI formulae for determining individual change on CNS VS' domain scores between T0 – T3

CNS VS domain	RCI-formula
Verbal Memory	$\text{AdjRCI}_{\text{srb}} \text{ Verbal memory} = \frac{D_i - 0.82 + [1 - (4.55/4.37)](X_i - 52.04)}{\sqrt{(4.37^2 + 4.55^2)(1 - 0.43)}}$
Visual Memory	$\text{AdjRCI}_{\text{srb}} \text{ Visual memory} = \frac{D_i - -0.21 + [1 - (4.81/4.34)](X_i - 46.27)}{\sqrt{(4.34^2 + 4.81^2)(1 - 0.41)}}$
Psychomotor Speed	$\text{AdjRCI}_{\text{srb}} \text{ Psychomotor speed} = \frac{D_i - 0.99 + [1 - (23.50/20.42)](X_i - 179.05)}{\sqrt{(20.42^2 + 23.50^2)(1 - 0.88)}}$
Reaction Time <sup>a</sup>	$\text{AdjRCI}_{\text{srb}} \text{ Reaction time} = \frac{D_i - -16.77 + [1 - (67.86/68.24)](X_i - 632.06)}{\sqrt{(68.24^2 + 67.86^2)(1 - 0.78)}} * -1$
Complex Attention <sup>a</sup>	$\text{AdjRCI}_{\text{srb}} \text{ Complex attention} = \frac{D_i - -0.76 + [1 - (4.07/4.30)](X_i - 6.44)}{\sqrt{(4.30^2 + 4.07^2)(1 - 0.55)}} * -1$
Cognitive Flexibility	$\text{AdjRCI}_{\text{srb}} \text{ Cognitive flexibility} = \frac{D_i - 3.77 + [1 - (12.14/11.37)](X_i - 46.90)}{\sqrt{(11.37^2 + 12.14^2)(1 - 0.74)}}$
Processing Speed	$\text{AdjRCI}_{\text{srb}} \text{ Processing speed} = \frac{D_i - 1.81 + [1 - (13.09/11.47)](X_i - 57.66)}{\sqrt{(11.47^2 + 13.09^2)(1 - 0.81)}}$

<sup>a</sup> Higher raw scores on Reaction Time and Complex Attention indicate lower performance, for all other domains, higher raw scores represent higher performance. Therefore, RCI values for Reaction time and Complex Attention must be multiplied by -1 to facilitate consistent interpretation of change on each cognitive domain

**Box 1.** Application of RCI formulae and a real-life example

<p>1. Subtract the assessed person's raw baseline test-score (<math>X_i</math>) from the raw retest-score (<math>Y_i</math>): this will result in a difference score (<math>D_i</math>).</p>	<p>Consider a person with a baseline score of 57 (<math>X_i</math>) and a retest score of 73 (<math>Y_i</math>) on Cognitive Flexibility. The calculated difference score (<math>D_i</math>) is 16.</p>
<p>2. Complement the RCI formula with the person's difference score, and the pretest score:</p> $\text{AdjRCI}_{\text{srb}} = \frac{D_i - D_c + [1 - (S_y/S_x)](X_i - X_c)}{\sqrt{(S_x^2 + S_y^2)(1 - r_{xy})}}$ <p><math>D_i</math> = Difference score: posttest score – pretest score of an individual  <math>D_c</math> = Difference score of the control group: mean posttest score – mean pretest score  <math>S_x, S_y</math> = SD of the pretest (x) and posttest (y) scores of the control group  <math>X_i</math> = Pretest score of an individual  <math>X_c</math> = Mean pretest score of the control group  <math>r_{xy}</math> = Test-retest reliability coefficient of pre- and posttest</p>	<p>We complement the RCI formula with the person's difference score and pretest score:</p> $\text{AdjRCI}_{\text{srb Cognitive Flexibility}} = \frac{D_i - 3.77 + [1 - (12.14/11.37)](X_i - 46.90)}{\sqrt{(11.37^2 + 12.14^2)(1 - 0.74)}}$ <p style="text-align: center;">↓</p> $\text{AdjRCI}_{\text{srb Cognitive Flexibility}} = \frac{16 - 3.77 + [1 - (12.14/11.37)](57 - 46.90)}{\sqrt{(11.37^2 + 12.14^2)(1 - 0.74)}}$ <p style="text-align: center;">= 1.36</p>
<p>3. Interpret the person's RCI, for example by applying the 90% confidence interval (CI): RCI values that fall within the 90% CI can be classified as 'stable' on this cognitive domain, whereas values outside the CI (i.e., <math>\pm 1.645</math>) can be denoted as having significantly 'improved' or 'declined'.</p>	<p>An RCI value of 1.36 falls within the 90% CI and the person's performance over time (despite the apparent improvement from 57 to 73) is therefore interpreted as 'stable'.</p>

**DISCUSSION**

Various clinical and research settings require repeated neuropsychological assessment, for example to evaluate the course of a disorder or the effects of an intervention on cognitive functioning. In the current study, test-retest reliabilities and practice effects for the frequently used computerized neuropsychological battery CNS VS were examined in sample of healthy Dutch participants.

The results demonstrated heterogeneous test-retest reliability coefficients for cognitive domains as well as test scores, thereby only partly supporting their stability in follow-up assessments over time. Test-retest reliability coefficients in the current study were generally consistent with those documented by prior studies on CNS VS' test-retest

reliability<sup>1,13,14</sup>, and with other studies that examined other computerized neuropsychological assessment tools.<sup>28</sup> In accordance with paper-and-pencil neuropsychological tests and the abovementioned studies, the lowest test-retest reliabilities were observed on measures of memory, as opposed to domains reflecting speed and reaction time, where test-retest reliabilities were high.<sup>29,30</sup> This common finding of relatively poor reliability for scores on memory tests has been attributed to the increased variability of memory as a construct in comparison with other cognitive functions<sup>29,30</sup>, rather than to unreliable test instruments. Nevertheless, one should put additional effort in the interpretation of changes in performance on the memory domain, for example by examining aspects of memory with more than one test or by incorporating measures of reliability in the determination of changes in performance.

Practice effects were demonstrated on three out of seven cognitive domains: higher performance on Cognitive Flexibility, Processing Speed, and Reaction Time was found at the three-month retest compared to the first assessment. No significant changes in performance were demonstrated between the second and third assessment. Previous research also demonstrated that practice effects predominantly occur between the first and second assessment, but diminish after the second assessment.<sup>10,14</sup> Practice effects may result from several factors, for example due to setting familiarity, task familiarity (e.g., including gaining comprehension of directions and knowledge of the sequence of a task), and familiarity with specific items (e.g., memorization of words on a list). Although CNS VS employs random presentation of stimuli from a reservoir of words and figures, the literature reports limited support for the effectiveness of precluding practice effects by using alternate forms of tests (e.g.,<sup>31</sup>). Indeed, our results suggest that practice effects were not fully precluded by the alternate forms of CNS VS. Future studies might for example consider the use of a multiple baseline design to control for effects of practice (e.g.,<sup>32,33</sup>). Results of the current study are also in line with previous findings on types of tests that suffer from practice effects, namely novel challenging cognitive tasks (e.g., Stroop Test and Symbol Digit Coding Test).<sup>30,34</sup>

Although in the literature several participant characteristics have been associated with variability in the magnitude of practice effects (i.e., practice effects becoming smaller with increased age (e.g.,<sup>35</sup>), or becoming larger with higher education (e.g.,<sup>10,36</sup>), we found no evidence that either age, education, or test interval is associated with variability in effects of practice regarding performance on CNS VS.

Use of raw difference scores for interpretation of change in individuals may not provide a reliable and unbiased picture, because of the imperfect test-retest correlations as well as the practice effects that we found with regard to repeated assessment using CNS VS that confound interpretation of these change scores. With the presented RCI-formulae specifically related to performance on the computerized battery CNS VS in a Dutch sample,

we provide a standardized method for addressing cognitive change over time whilst taking methodological issues such as practice effects into account. By presenting RCI formulae we do not only aim to provide a solution for interpreting performance in Dutch participants when CNS VS is used repeatedly over time, but we also hope for employment of this approach into clinical practice and in future studies examining other neuropsychological measures over time. Although our results may not be generalizable to other countries or populations who speak other languages, they demonstrate that CNS VS users should be cautious when interpreting performance on repeated assessments using the original American norms. As for our own research and clinical practice, we will from now on incorporate the RCI into our ongoing patient studies, in which we evaluate the course and effects of surgery in patients with brain tumors.

A few limitations to the interpretation and application of the presented results should be discussed. First, CNS VS may be self-limiting in its ability to show practice effects over time. Ceiling effects of the test may limit improvements in performance – for example, a potential ceiling effect was reached for the Continuous Performance Test from upon the first test administration (i.e., raw mean score was 39.94 at T0 whereas the highest achievable score for this particular test is 40). However, since we did not observe clear ceiling effects on other tests, this factor is unlikely to explain findings with regard to (the absence of) practice effects for some domains in the current study. Second, the findings presented in this study are based on performance in healthy Dutch participants recruited on availability (i.e., convenience sampling). Preventing participants from dropping out of the study before completion of all follow-up assessments proved to be challenging, which might partly be explained by the fact that participants did not receive a compensation for participation in the study. These factors may have caused selection and retention biases, although no significant differences between the sociodemographic characteristics and baseline cognitive performance of participants who completed all assessments and of participants who dropped out were demonstrated. Thirdly, a relatively small number of low educated participants (i.e., 12% compared to approximately 35% in the general Dutch population<sup>37</sup>) was included in the present sample. Yet, no significant importance with regard to the effects of educational level on change scores between the first and second, and second and third assessment was found. One should be aware that results might not be generalizable to (clinical) populations with much lower levels of education. However, one should always be careful when interpreting (changes in) individual test performance of people who are in the extreme ends of education or other predictor variables. Fourth, the test-retest intervals in our study varied considerably amongst subjects and were also relatively long compared to other studies involving repeated assessments using CNS VS (e.g.,<sup>13,14</sup>). Within this longer timeframe, systematic error, random error and real changes in cognitive function are more likely to have occurred. To control for the impact of these systematic and random errors, we

computed ICCs for agreement and established RCI-formulae. Since the test-retest interval used in this study closely approximated the design of our ongoing patient studies (e.g.,<sup>7</sup>), this relatively long interval was still preferred.

Although repeated neuropsychological assessment is of great value both in clinical and research settings, the interpretation of change in performance at retesting can be challenging. With regard to repeated assessment using CNS VS, we found imperfect test-retest reliabilities and practice effects for some of its domains in a Dutch sample. As previous research shows, these issues also impact the interpretation of performance on other computerized, as well as conventional paper-and-pencil, neuropsychological tests, we expect that many clinicians and researchers face these difficulties. This clearly highlights the need for methods that evaluate individual change in performance over multiple assessments whilst accounting for imperfect test-retest reliabilities and practice effects. Establishing RCI-formulae for specific populations and tests may be a practical method for determining individual reliable change in future longitudinal scientific or clinical work facing the methodological issues of repeated testing.

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## CHAPTER 3

# Assessment of executive functioning in patients with meningioma and low-grade glioma: A comparison of self-report, proxy-report and test performance



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## ABSTRACT

**Objective:** This study aimed to examine 1) patient-proxy agreement on executive functioning (EF) of patients with primary brain tumors, 2) the relationships between patient- and proxy-report with performance-based measures of EF and 3) the potential influence of performance-based measures on the level of agreement.

**Method:** Meningioma and low-grade glioma patients and their informal caregivers completed the Behavior Rating Inventory of Executive Function (BRIEF-A) three months after surgery. The two index scores of the BRIEF-A, Behavioral Regulation and Metacognition, were evaluated. Mean scores of patients and proxies were compared with normative values and with each other. Patient-proxy agreement was evaluated with Lin's concordance correlation coefficients (CCCs) and Bland-Altman plots. Pearson correlation coefficients between reported EF and performance-based measures of EF were calculated. Multiple regression analysis was used to evaluate the potential influence of test performance on differences in dyadic reports.

**Results:** A total of 47 dyads were included. Patients reported significantly more problems on the Metacognition index compared to norms, and also in comparison with their proxies. Effect sizes indicated small differences. Moderate to substantial agreement was observed between patients and proxies, with CCCs of .57 and .61 for Metacognition and Behavioral Regulation respectively. Correlations between reported EF and test performance ranged between -.37 and .10. Dyadic agreement was not significantly influenced by test performance.

**Conclusions:** Patient-proxy agreement was found to be moderate. No clear associations were found between reported EF and test performance. Future studies should further explore existing and new methods to assess everyday EF in brain tumor patients.

## INTRODUCTION

Over the last few decades, patients and their family members are increasingly being involved in care decisions.<sup>1,2</sup> To be able to make informed decisions, patients need sufficient cognitive abilities and self-awareness, but these functions can be disturbed in patients with brain disorders (e.g.,<sup>3-5</sup>). More specifically, evidence emerging from patient studies, imaging research and behavioral paradigms suggests that different components of executive functioning (EF) play a crucial role in decision making and that impairments in EF seem to be associated with risky and ambiguous decision making.<sup>6-8</sup> Executive functions include several higher-order cognitive processes that enable people to control and regulate their own behavior. Key executive functions are inhibition (i.e. deliberate overriding of dominant responses), cognitive flexibility (i.e. shifting between different tasks or mental sets) and working memory (i.e. constant monitoring and updating of retained information).<sup>9-11</sup> With respect to decision making, executive functions are necessary for, amongst others, assessing probabilities, categorizing options, selecting decision making strategies and using feedback to revise strategies if necessary.<sup>8</sup>

Impairments in EF are amongst the most pronounced cognitive deficits in patients with primary brain tumors.<sup>12-15</sup> Impairments in EF can have a negative impact on patients' everyday lives, but also on the lives of the people in their environment.<sup>16-18</sup> It is important to identify problems with EF at an early stage, so we can refer to intervention programs in time, including for example Goal Management Training (GMT).<sup>19</sup>

From research and clinical practice, it is known that patients who experience cognitive complaints, do not necessarily show lower scores on neuropsychological tests. And vice versa, if patients demonstrate lower test performance, they do not always experience cognitive complaints in their daily life.<sup>20,21</sup> Therefore, both neuropsychological tests and self-report questionnaires on EF are often used to get a full picture of a person's EF. When patients are unable to complete assessments, due to for example language problems or paralysis, information from informal caregivers can be of added value. When using proxy-report as an addition to, or as a substitute for self-report, it is crucial to know how these measures are related.

A few studies in brain tumor patients evaluated patient-proxy agreement with respect to patients' quality of life. Overall, moderate to high levels of concordance were observed, if patients did not suffer from cognitive dysfunction.<sup>22-25</sup> Also, high congruence was found in the study of Armstrong et al. on a brain tumor symptom checklist (MDASI) that was administered in 115 brain tumor patients and their caregivers.<sup>26</sup> Additionally, a study in 60 brain tumor patients showed high level of agreement between patients and proxies on the Dexamethasone Symptom Questionnaire-Chronic.<sup>27</sup> By contrast, the study of Rooney and colleagues demonstrated substantial disagreement between glioma patients and their proxies in the evaluation of depressive symptoms, with proxies reporting more

depressive symptoms than patients themselves.<sup>28</sup> These authors suggested that patients and proxies generally seem to agree on objective signs and overt behavior of patients, but that agreement is limited on subjective, internal symptoms, such as mood and emotional functioning.<sup>28</sup>

It is important to know how brain tumor patients perceive their EF, and how this relates to the experience of their informal caregivers and to performance-based measures of EF. In the current study, the main objective was to evaluate the level of agreement between patient-report and proxy-report of patients' EF. Second, associations of reported measures of EF with performance-based measures of EF (i.e., neuropsychological tests) were examined, as well as the influence of these performance-based measures on the level of patient-proxy agreement. Since from previous studies it is known that brain tumor patients suffer from executive deficits, we hypothesized that this may also influence their self-assessment, potentially resulting in disagreement among patients and proxies. We also expected that lower patients' scores on performance-based measures would be associated with greater patient-proxy discrepancies.

## **METHOD**

### **Design & procedure**

Data of this study were gathered at pre-intervention assessments in a feasibility study<sup>29</sup> and a randomized controlled trial<sup>30</sup> on cognitive rehabilitation in brain tumor patients, initiated at the Elisabeth-TweeSteden Hospital Tilburg, The Netherlands. This research was conducted in accordance with the Declaration of Helsinki.<sup>31</sup> The cognitive rehabilitation study (i.e., feasibility study and RCT) was approved by the local ethical review board (METC Brabant: NL 51152.028.14) and registered with clinicaltrials.gov (NCT03373487) and the Dutch Trial Register (NTR5392).

Before and three months after surgery, patients underwent neuropsychological assessment (NPA) as part of usual clinical care in the hospital. Directly after the 3-month NPA, patients who participated in the randomized controlled trial were randomized to an intervention or control condition. During an appointment with the researcher three months after surgery, participants and proxies completed the adult version of the Behavior Rating Inventory of Executive Function (BRIEF-A).<sup>32</sup>

### **Participants**

Adult patients who were scheduled for resective surgery for a meningioma or low-grade glioma, were invited to participate in one of the cognitive rehabilitation studies. Patients undergoing only biopsy were not eligible. Exclusion criteria were tumor resection in the last year; chemotherapy or radiotherapy in the last two years; presence/history of progressive

neurological disease; severe psychiatric disorder or substance abuse; diagnosis of acute neurological or mild psychiatric disorders in the last two years (e.g., CVA); multiple (>1) tumors; lack of basis proficiency in Dutch; Karnofsky Performance Score below 70; IQ below 85 or (very) low cognitive skills; and insufficient reading skills, visual impairment, or motor impairment. Patients were also excluded if they had severe surgery-related complications or if they were referred to formal cognitive rehabilitation.

Study participants were invited to involve an informal caregiver (e.g., spouse, family member or close friend) to the study. No exclusion criteria were applied to the proxies. If patients agreed, informed consent was obtained from the proxies. Only participants who involved an informal caregiver were included in the present analyses.

## Measures

The BRIEF-A assesses problems in an adult's EF as experienced in his or her daily life.<sup>32</sup> A self-report and informant-report version are available and both questionnaires consist of 75 items. Patients and proxies were asked to assess the extent to which certain behavior of the patient occurred during the past month. The informant version of the BRIEF-A uses a proxy-proxy perspective: proxies need to report on how they think the patient is functioning. Answers are given on a three-point scale (i.e., never = 1, sometimes = 2, often = 3). Two index scores, Behavioral Regulation and Metacognition, can be calculated based on 30 and 40 items respectively. Behavioral Regulation contains four subscales (i.e. Inhibit, Shift, Emotional Control and Self-monitor), and Metacognition has five subscales (i.e. Initiate, Working Memory, Plan/Organize, Task-monitor, and Organization of Materials). Three validity scales (i.e., Negativity, Infrequency and Inconsistency) were checked, and in case of invalid responses, patients were excluded from analyses. Cases were also excluded if there were  $\geq 5$  missing answers. Missing values were handled in accordance with the manual<sup>33</sup> and scores of "1" were imputed in case of missing values. Raw scores on the indices were converted into *T* scores, using representative norms of the Dutch/Flemish population (self-report:  $n = 1600$ , informant-report:  $n = 1082$ ).<sup>33</sup> These standardized *T* scores were converted into *Z* scores and also reversed, to coincide with performance-based scores, so that lower *Z* scores indicate lower subjective EF. *Z* scores  $\leq -1.5$  were considered as low.<sup>33</sup> Psychometric properties of the Dutch version of the self-report and informant-report are good, with Cronbach's alphas above 0.90 and intra-class correlation coefficients between 0.73 and 0.81, for the two indices.<sup>33</sup>

Three neuropsychological tests from the 3-month assessment were included to measure different aspects of performance-based EF. Response inhibition and cognitive flexibility were measured, respectively, with the Stroop Test and the Shifting Attention Test (SAT) of the computerized test battery Central Nervous System Vital Signs (CNS VS, LCC, Morrisville, North Carolina). Regarding validity and reliability, Gualtieri and Johnson (2006)

concluded that psychometric characteristics of the CNS VS' tests were comparable with the conventional tests on which they were based.<sup>34</sup> Additionally, previous studies demonstrated sufficient sensitivity of the CNS VS in the detection of (mild) cognitive deficits and change in cognitive function in patients with brain tumors.<sup>35-37</sup> Furthermore, the Digit Span Backward of the Wechsler Adult Intelligence Scale (WAIS-III)<sup>38</sup> was used to assess working memory. Patients' scores on the neuropsychological tests were compared to representative, recently collected Dutch norms.<sup>39-41</sup> Patient test scores were corrected for sex, age, educational level and practice effects, and converted into Z scores, with lower scores indicating worse EF performance. Again, Z scores  $\leq -1.5$  were considered as low.

### Data analysis

Descriptive statistics of the sample were calculated and compared with patients who were not included in the current study (i.e. patients who did not include a proxy in the cognitive rehabilitation study) using independent-samples *t*-tests and Chi-square tests.

Mean scores of patients and proxies were compared with normative values ( $M=0$ ,  $SD=1$ ) using two-tailed one-sample *z*-tests. The standardized mean differences between patients and the normative values, and those between proxies and normative values, are interpreted as Glass' delta effect sizes, with 0.20-0.49 indicating small effects, 0.50-0.79 medium effects, and  $\geq 0.80$  reflecting large effects.<sup>42</sup> Subsequently, means of the patients were compared with means of the proxies using two-tailed paired-sample *t*-tests, to investigate potential systematic differences, and effect sizes (Cohen's  $d^{43}$ ) were calculated.

To examine the level of concordance between patient- and proxy-reports, Lin's concordance correlation coefficients (CCCs)<sup>44,45</sup> were calculated for the two indices of the BRIEF-A. CCCs were interpreted as follows: 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 almost perfect to perfect agreement.<sup>46</sup> As described in the manual of the BRIEF-A<sup>33</sup>, in order to be able to consider patient-report and proxy-report as interchangeable, ICC's of at least 0.60 are required. Bland-Altman plots were generated, plotting the difference between measurements (i.e. patient score - proxy score) against the mean of the two measurements (i.e.,  $(\text{mean patient score} + \text{mean proxy score})/2$ ).<sup>47</sup> By visualizing these differences, patterns of agreement, types of bias and outliers can be further identified. We computed 95% confidence envelopes around the mean difference (i.e.,  $\text{mean} \pm 1.96 \times \text{SD of difference scores}$ ), which shows the range of difference scores that covers 95% of the observations. Patient and proxy scores can be used interchangeably if the range is small given the application envisaged. Furthermore, patient and proxy scores on the two indices were dichotomized denoting low (Z score  $\leq -1.5$ ) or normal (Z score  $> -1.5$ ) EF. Percentages of cases below the cut-off were calculated and percentages of dyadic agreement about the presence or absence of reported EF impairment were determined.

Furthermore, performance-based measures of EF were examined, with standardized mean scores of the patients being compared to normative values ( $M = 0$ ,  $SD = 1$ ) with  $z$ -tests. The relationship between performance-based measures of EF and reported EF was explored by calculating Pearson's product moment correlation coefficients between standardized performance scores and index scores of both patients and proxies. Correlation coefficients between 0.10 and 0.29 were considered as small, 0.30-0.49 were considered as medium, and 0.50-1.0 reflected large correlation coefficients.<sup>43</sup>

Finally, the association between objective EF and the level of agreement was examined using multiple regression analysis. The observed difference scores (patient self-report - proxy-report score) on the two BRIEF-A indices served as the dependent variables. All independent variables (standardized scores on the Stroop Test, Shifting Attention Test and Digit Span Backward of the 3-month NPA) were entered at the same time for each of the two analyses. Assumptions were evaluated using Durbin-Watson tests<sup>48</sup>, scatterplots and histograms of residuals, variance inflation indices (not exceeding 0.80 and 10)<sup>49</sup> and Cook's distances ( $\leq 1$ )<sup>50</sup>.

Statistical analyses were conducted using SPSS Statistics (version 24.0). All statistical tests were performed at an alpha level of .05.

## RESULTS

### Participants' characteristics

Three months after surgery, 47 out of 75 participants (63%) of the cognitive rehabilitation studies chose to involve a proxy. Regarding age, years of education, sex, tumor histology and patient-reported EF, no significant differences were observed between patients who did include a proxy and those who did not ( $p$ -values  $> .05$ ). Included patients ( $n = 47$ ) had a mean age of 51 years and 26 patients (55%) were female. Twenty-eight patients (60%) were diagnosed with a meningioma and 19 (40%) with a low-grade glioma. In 26 patients (55%), the tumor was located in the frontal lobe. In the large majority (94%), the relationship of the proxy to the patient was partner. Three patients involved their mother, sister or brother.

All BRIEF-A questionnaires met the validity criteria. There were no questionnaires with  $\geq 5$  missing values. In this study, Cronbach's alphas of the indices ranged between .90 and .96 in patients and proxies, indicating good internal consistency.<sup>51</sup>

### Patient-report and proxy-report of patients' EF

Patients scored on average significantly lower on the Metacognition index in comparison with normative values ( $M = -0.47$ ,  $SD = 1.04$ ,  $z = -3.25$ ,  $p = .001$ ). Glass' delta effect size of 0.47 suggested a small effect. On the Behavioral Regulation Index, the average patient score did not significantly differ from normative values ( $M = 0.02$ ,  $SD = 1.01$ ,  $z = 0.13$ ,



$p = .896$ ). There were no significant differences between proxy evaluations of patients' EF and normative values for both indices (Table 1).

When comparing mean patient scores with mean proxy scores using paired-sample  $t$ -tests (Table 1), a significant mean difference was observed on the Metacognition Index. Patients reported significantly lower EF (i.e. more concerns) than their proxies ( $t(46) = -2.40$ ,  $p = .021$ , Cohen's  $d = -0.35$ ), with Cohen's  $d$  indicating a small effect. On the Behavioral Regulation index, no significant mean difference was observed between patients and proxies ( $t(46) = -0.83$ ,  $p = .703$ , Cohen's  $d = -0.06$ ).

On the Metacognition and Behavioral Regulation index, 23% and 9% of the patients scored below the cut-off ( $Z$  score  $\leq -1.5$ ), respectively. According to the report of the proxies, 13% and 6% of the patients would score below the cut-off of the Metacognition index and Behavioral Regulation index respectively.

### **Level of agreement between patients and proxies**

Lin's CCCs, listed in Table 2, indicated moderate to substantial agreement among patients and proxies (CCCs of 0.57 for Metacognition and 0.61 for Behavioral Regulation). Figure 1 shows the Bland-Altman plots. The lower and upper limits were -2.11 and 1.47 for Metacognition and -1.76 and 1.67 for Behavioral Regulation. The Bland-Altman plots showed that 93.6% of the data points (i.e. 44/47) lied within these limits of agreement. Inspection of the plots revealed no particular trends in agreement with respect to the level of reported EF. When the cutoff for reported EF impairment (i.e.  $Z$  score  $\leq -1.5$ ) was applied, congruence was observed in 94% (44/47) dyads on Behavioral Regulation and in 77% (36/47) dyads on Metacognition (Table 3). Based on the dichotomized data of the Metacognition index, 8 proxies of the 11 non-agreeing dyads did not rate the patient's EF as impaired, whereas the patient did (Table 3).

Table 1. Mean levels of reported EF: Comparison with normative values and differences between patients (n = 47) and proxies (n = 47)

BRIEF-A index	Mean (SD) Patients <sup>a</sup>	p-value <sup>b</sup>	Effect size	Mean (SD) Proxies <sup>a</sup>	p-value <sup>b</sup>	Effect size	Mean difference (SD) <sub>diff</sub>	p-value	Effect size
Behavioral Regulation	0.02 (1.01)	.896	0.02	0.07 (0.96)	.641	0.07	-0.05 (0.88)	.703	-0.06
Metacognition	-0.47 (1.05)	.001*	-0.47	-0.16 (0.98)	.287	-0.16	-0.32 (0.91)	.021*	-0.35

<sup>a</sup> Lower scores indicate lower reported EF/more experienced problems. Table 2. Level of agreement between patient-report and proxy-report of EF

Table 2. Level of agreement between patient-report and proxy-report of EF

		Bland Altman Analyses			
		Lins CCC			
BRIEF-A index	Lin's CCC <sup>b</sup>	CCC's 95% CI	Limits of Agreement <sup>c</sup>	% < limit	% > limit
Behavioral Regulation	.61	.39-.76	-1.76; 1.67	2.1%	4.3%
Metacognition	.57	.35-.73	-2.11; 1.47	2.1%	4.3%

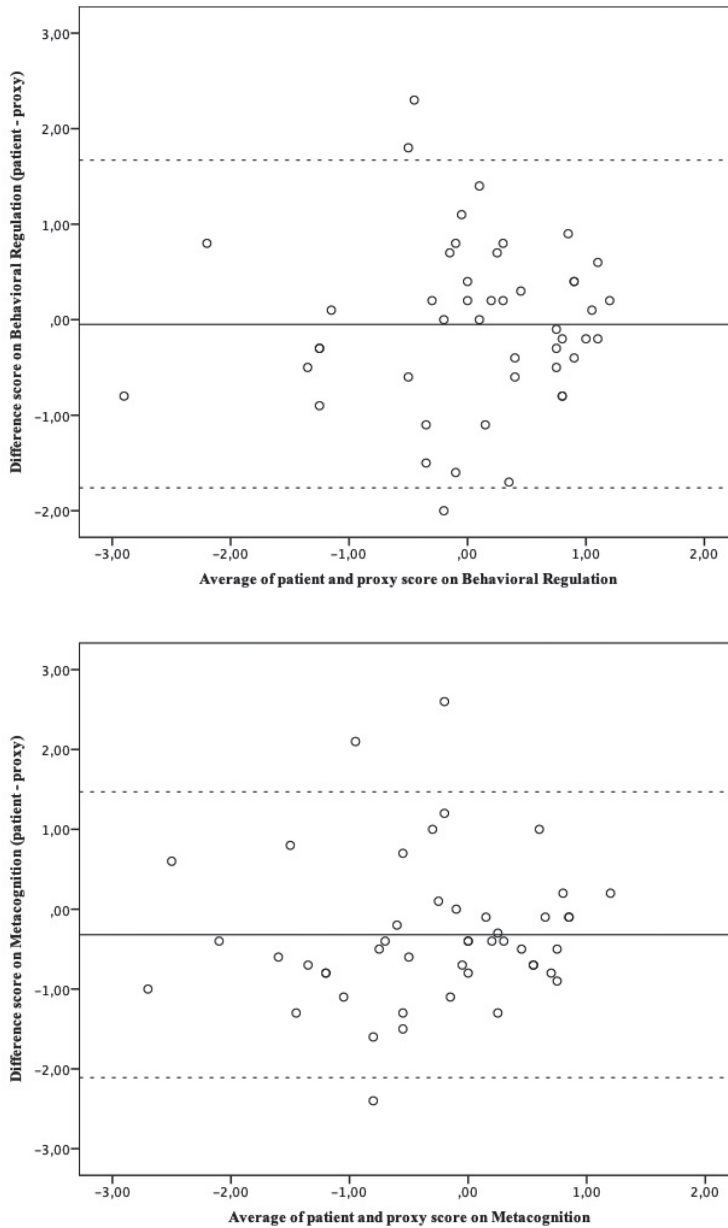
<sup>a</sup> 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, 0.81–1.00 almost perfect to perfect agreement.<sup>46</sup>

<sup>b</sup> Limits of Agreement: Mean<sub>diff</sub> ±1.96\*SD<sub>diff</sub>

**Table 3.** Dyadic agreement on the presence or absence of reported EF impairment

Behavioral Regulation				
		Patient Score		
		Non-impaired	Lower reported EF	Total
Proxy Score	Non-impaired	42	2	44
	Lower reported EF	1	2	3
	Total	43	4	47
Metacognition				
		Patient Score		
		Non-impaired	Lower reported EF	Total
Proxy Score	Non-impaired	33	8	41
	Lower reported EF	3	3	6
	Total	36	11	47

Note: Z scores  $\leq -1.5$  were considered as low.<sup>33</sup>



**Figure 1:** Bland-Altman plot for agreement on the a) Behavioral Regulation index, and b) Metacognition index

Note: Dashed lines represent the upper and lower limit of the 95% confidence intervals

### **Performance-based versus reported EF**

Compared to normative values of the general population, patients scored significantly lower on the Stroop Test ( $M = -0.91$ ,  $SD = 1.71$ ,  $z = -6.25$ ,  $p < .001$ ), the Shifting Attention Test ( $M = -1.09$ ,  $SD = 1.34$ ,  $z = -7.26$ ,  $p < .001$ ) and Digit Span Backward ( $M = -0.84$ ,  $SD = 0.96$ ,  $z = -75$ ,  $p < .001$ ) three months after surgery (Table 3).

Using a cut-off of  $Z \leq -1.5$ , 15 patients (32%) had low scores on the Stroop Test, 14 (30%) on the Shifting Attention Test and 12 (26%) patients scored low on Digit Span Backward. In total, 31 patients (66%) had  $Z$  scores  $\leq -1.5$  on one or more tests.

Correlation coefficients of neuropsychological tests scores with patient-report and proxy-report are listed in Table 4. Overall, non-significant very small correlations were observed, with  $r$ 's ranging from  $-0.29$  to  $0.10$ , except for Digit Span Backward, where significant negative correlations were observed with patient-report of EF ( $r$ 's of  $-0.33$  and  $-0.37$  for Behavioral Regulation and Metacognition respectively).

### **Association between EF test performance and patient-proxy differences**

Multiple regression analyses indicated that scores on performance-based measures of EF (Stroop Test, Shifting Attention Test and Digit Span Backward) had no significant influence on the patient-proxy difference scores of Behavioral Regulation ( $F(3,47) = 0.109$ ,  $p = .954$ ,  $R^2 = .008$ ) and Metacognition ( $F(3,47) = 0.924$ ,  $p = .412$ ,  $R^2 = .065$ ).

**Table 4.** Performance-based measures of EF: Mean scores compared to normative values and correlations with reported EF

Neuropsychological test	Domain	Mean (SD)	p-value <sup>a</sup>	Effect size	Patient-report		Proxy-report	
					Behavioral Regulation <sup>b</sup>	Metacognition <sup>b</sup>	Behavioral Regulation <sup>b</sup>	Metacognition <sup>b</sup>
Stroop Test	Inhibition	-0.91 (1.71)	<.001*	0.91	-.10	.10	-.14	.03
Shifting Attention Test	Cognitive flexibility	-1.06 (1.34)	<.001*	1.06	-.17	-.13	-.15	-.04
Digit Span Backward	Working memory	-0.84 (0.96)	<.001*	0.84	-.33*	-.37*	-.29	-.021

<sup>a</sup> Sample means compared to normative values (Mean = 0, SD = 1).

<sup>b</sup> Correlation coefficients between .10 and .29 were considered as small, .30-.49 as medium, and .50-1.0 as large.<sup>43</sup>

## DISCUSSION

The present study was performed to evaluate patient-proxy agreement with respect to report of executive functioning (EF) in patients with meningioma and low-grade glioma. In addition, the relationship between reported EF with performance-based measures of EF was investigated, as was the effect of EF test performance on the level of agreement. Since patients are increasingly involved in health-care decisions, it is important to gain more insight in their metacognitive abilities, and, how their experiences relate to experiences of their informal caregivers and to performance-based measures of EF.

Firstly, compared to normative data, lowered patient scores were observed on reported EF (Metacognition index) and on EF test performance (Stroop Test, Shifting Attention Test and Digit Span Backward). These findings contribute to the large body of evidence showing that patients with primary brain tumors experience complaints and deficits in EF after neurosurgery. Moreover, it stresses the importance of careful assessment of EF. Since problems in EF can have major impact on everyday life of patients and health care decisions, attention should be paid to EF of patients throughout their disease trajectory, in both clinical care and research settings.

In this study, patients reported significantly more problems than their proxies on the Metacognition index. A similar mismatch between patients and partners has been reported in patients with dementia. It has been suggested that in the early stages of the disease, patients experience subtle cognitive complaints, that are not always noticed by their partners (e.g.,<sup>52,53</sup>). However, when the disease progresses, diminished disease awareness often arises<sup>5</sup>, leading to the reversed pattern: partners often report more problems than patients.<sup>52</sup> Our sample consists of brain tumor patients who have slow-growing tumors and a relatively favorable prognosis. It is possible that self-reported EF problems may decrease as the disease progresses and that studies in patients with high-grade glioma or metastases with less favorable prognosis would render different results. However, more research is needed to further explore this hypothesis. Furthermore, no systematic differences between patients and proxies were observed in group means of the Behavioral Regulation index. Possibly, this is due to the fact that this index generally contains more items that are aimed at the report of concrete, overt behavior (e.g., “I drum my fingers or wiggle my legs”; “I start things on the last moment”), which makes it easier for proxies to assess patients’ functioning.<sup>28</sup>

Regarding the degree of concordance as measured with Lin’s CCCs, findings indicate moderate to substantial agreement among dyads on patients’ EF, with CCCs of .61 and .57 for the Behavioral Regulation index and Metacognition index. Based on these CCCs, we can conclude that proxy-reports are a reasonable estimate of patient-reported EF. The additional information from the Bland-Altman plots and cross tables, suggests less agreement between patients and proxies on the Metacognition index compared to

the Behavioral Regulation index. This can also be explained by the more concrete and observable symptoms assessed by the Behavioral Regulation index, as described above.

Although patients showed lower EF test scores, no clear associations were observed between patients' self-reports and proxy reports with performance-based measures of EF. Overall, (very) small correlations were observed in this study, which is in line with previous research in brain tumor patients and other neurologic populations.<sup>54-57</sup> Based solely on the absence of associations of patients' self-report and performance-based results, one might conclude that patients are not able to estimate the objective level of their EF, possibly due to a lack of insight or reduced cognitive capabilities. However, the current findings render this explanation more unlikely, since we found that there was concordance between patient and proxies, and proxy-report was also not significantly correlated with patients' test performance. Thus, there is a mismatch between reported EF and test performance, but we do not know which of the measures is the most accurate.

There are many difficulties involved in measuring EF, and an objective gold standard is missing. Based on the finding that reported EF was not correlated with EF test performance in both clinical and non-clinical samples, Toplak and colleagues concluded in their review that rating measures of EF and performance-based measures of EF appear to capture different underlying mental constructs and therefore, they cannot be interpreted as equivalent nor be used interchangeably.<sup>58</sup> Tests often focus on a particular domain of EF and are administered in a quiet and controlled environment on a certain moment in time, while EF in everyday life requires complex, integrated and dynamic skills. Ecological validity of performance-based measures of EF is limited, and thus will not fully capture experienced problems in patients' day-to-day functioning. On the other hand, several studies demonstrated that self-reported EF is associated with psychological variables, such as personality and mood<sup>56,59,60</sup> and that self-report response biases can affect validity and reliability.<sup>61</sup>

In addition to neuropsychological tests, Noll and colleagues made use of measures of functional independence (i.e. the Functional Independence Measure and the Karnofsky Performance Status) and found significant correlations between functional independence and performance-based measures of EF ( $r$ 's between .28 and .42).<sup>62</sup> A potential promising alternative is using an Experience Sampling Method (ESM) to measure self-reported EF, at multiple times throughout the day, actually integrated in the daily lives of patients.<sup>63,64</sup> By gathering real-time data, some biases that occur through reporting in retrospect on conventional self-report questionnaires can be avoided. Furthermore, virtual environments (VE) are increasingly being used to enhance neuropsychological testing, so that they better reflect situations patients face in the outside world.<sup>65,66</sup> These relatively new assessment techniques, with potentially improved validity and reliability, could also be explored in future studies in patients with primary brain tumors.



In this study, no effect of executive test performance on dyadic agreement was found, which is in contrast with our expectations based on previous research on health-related quality of life in brain tumor patients<sup>22,24,25</sup> and studies in other populations<sup>67,68</sup>. It should be noted that the instruments used to assess cognitive performance differed across studies (e.g. the Mini Mental State Examination or extensive neuropsychological test batteries), as well as the statistical procedures used to examine the possible effect of test performance on dyadic agreement. Moreover, it is possible that deficits in EF are more likely to relate to patient-proxy agreement when patients report *less* problems than proxies (potentially resulting from impaired insight), instead of *more* problems, as was observed in our sample of meningioma and low-grade glioma patients.

Besides EF test performance, other factors may also have modulated the level of agreement between patients and proxies, including patient- or disease-related factors, proxy-related factors or factors related to the assessment of EF. The small sample size of this study limited our possibilities to explore the potential influence of, for example tumor location or tumor histology, with valid statistical testing. Also, we had little information available on the informal caregivers or the quality of the relationship with the patient, restricting the possibility to take this into account. Moreover, informal caregivers were involved in the cognitive rehabilitation study, *only* if patients (and proxies) were willing to. Possibly, this may have led to a selection bias (i.e. sampling bias), namely the inclusion of dyads who are highly motivated and might agree on the patient's functioning more than dyads not included in this study. In addition, all patients in this study were participants in a cognitive rehabilitation trial, with strict in- and exclusion criteria, which may also hamper generalizability of the findings to the low-grade glioma and meningioma patient population as a whole.

In conclusion, patients with primary brain tumors experience executive deficits after neurosurgery. Congruence between brain tumor patients and their proxies was observed in the evaluation of patients' EF, but correlations with performance-based measures of EF were low. Since problems in EF are commonly observed in brain tumor patients, and can lead to lowered quality of life, it is important to assess EF carefully throughout the disease trajectory, using both questionnaires and performance-based measures of EF. At the same time, research on the use of innovative methods to assess EF in patients with primary brain tumors should be expanded.

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## CHAPTER 4

# Prevalence and correlates of fatigue in patients with meningioma before and after surgery



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## ABSTRACT

**Background:** Fatigue is a common symptom in patients with brain tumors, but comprehensive studies on fatigue in patients with meningioma specifically are lacking. This study examined the prevalence and correlates fatigue in meningioma patients.

**Methods:** Patients with grade I meningioma completed the Multidimensional Fatigue Inventory (MFI-20) before and one year after neurosurgery. The MFI consists of five subscales: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Patients' scores were compared to normative data. Preoperative fatigue was compared to postoperative fatigue. Correlations with sex, age, education, tumor hemisphere, preoperative tumor volume, antiepileptic drugs (AEDs), symptoms of anxiety/depression and self-reported cognitive complaints were explored.

**Results:** Questionnaires were completed by 65 patients preoperatively, and 53 patients postoperatively. Of 34 patients, data from both time-points were available. Patients had significantly higher fatigue levels on all subscales compared to normative values at both time points. Mean scores on General Fatigue, Physical Fatigue and Mental Fatigue remained stable over time and improvements were observed on Reduced Motivation and Reduced Activity. Preoperatively, the prevalence of high fatigue (Z-score  $\geq 1.3$ ) varied between 34% for Reduced Motivation and 43% for General Fatigue/Mental Fatigue. The postoperative prevalence ranged from 19% for Reduced Activity to 49% on Mental Fatigue. Fatigue was associated with cognitive complaints, anxiety and depression, but not with education, tumor lateralization, tumor volume or AEDs.

**Conclusion:** Fatigue is a common and persistent symptom in patients with meningioma undergoing neurosurgery. Findings emphasize the need for more research and appropriate care targeting fatigue for meningioma patients.

## INTRODUCTION

Meningiomas are for the most part slow-growing tumors that compress the surrounding, healthy brain and eventually may cause symptoms. They account for approximately one-third of all diagnosed primary central nervous system tumors.<sup>1</sup> Most meningiomas will remain asymptomatic and undetected during a person's lifetime, but a subset receives medical attention because of related symptoms (e.g. seizures or neurological deficits) or because they are coincidentally detected on a brain scan.<sup>2</sup> Observation (wait-and-scan), neurosurgical resection and (stereotactic) radiation therapy are the most common treatment options. The majority of meningiomas are benign (i.e. >90% WHO-grade I) and have a favorable long-term prognosis.<sup>1,3</sup> A distinct worse prognosis is generally observed in patients with atypical (WHO-grade II) or anaplastic (WHO-grade III) meningiomas. These tumors grow faster, are more likely to recur and may invade the brain.<sup>3</sup> It is a common clinical presumption that patients with grade I meningioma have the most favorable recovery in terms of quality of life and return to normal socioprofessional life. However, accumulating evidence indicates that a significant number of these patients experience cognitive deficits and lower quality of life, even long after treatment has ended.<sup>4,5</sup>

Fatigue is a very common symptom in patients with primary brain tumors, with prevalence estimates varying between 39% and 96%.<sup>6-8</sup> Fatigue is described as a subjective feeling of tiredness and a lack of energy.<sup>9</sup> It is a multidimensional construct, wherein a distinction can be made between physical and mental fatigue.<sup>10-11</sup> In healthy individuals, fatigue is a normal and adaptive response to physical or mental activities, which can be alleviated by periods of sleep or rest. However, in neurological and oncological patients, fatigue can be a persisting and/or relapsing symptom, which is not in proportion to recent activities and not adequately alleviated by rest.<sup>10-11</sup> Importantly, fatigue can substantially interfere with patients' personal and professional activities, and it can significantly lower patients' quality of life.<sup>6,12</sup>

Most of the research on fatigue in brain tumor patients has been conducted in patients with glioma, often malignant tumors that grow from glial or precursor cells in the brain.<sup>1</sup> These studies indicate that symptoms of fatigue are quite common already prior to treatment, and that they can persist several years thereafter.<sup>7,8,13,14</sup> Fatigue in glioma patients has been associated with various factors, including higher age, female sex, left-hemispheric location, radiotherapy, chemotherapy, the use of anti-epileptic drugs (AEDs) and opioids, psychological distress, sleep disturbances and cognitive complaints.<sup>7,15,16</sup>

Little research has been conducted on fatigue in patients with meningioma. Several studies on quality of life in patients with meningioma made use of instruments including a few items on fatigue (e.g.,<sup>17,18</sup>). In addition, a handful of studies evaluated the (side-) effects of (stereotactic) radiotherapy in which fatigue was one of the outcome measures.<sup>19-22</sup> These studies suggest that fatigue is present in patients with meningioma, but firm conclusions

cannot be drawn, because mostly heterogeneous samples or small samples of meningioma patients were included. Moreover, fatigue has never been included as a primary outcome and consequently, results regarding fatigue have not always fully been described, have not been described separately for patients with meningioma or not described at all. Also, a comparison with a control group has often been lacking, which may have distorted findings in patient samples, since fatigue is also a common complaint in the general population. Additionally, all previous studies assessed fatigue with single-item measures (yes/no), or with very brief unidimensional questionnaires or subscales whereas it is a multidimensional construct. As a consequence, there is insufficient understanding of the severity and type of fatigue in patients with meningioma.

This study evaluates fatigue, using a validated multidimensional questionnaire, in a select sample of patients with WHO-grade I meningioma, before surgery and one year after surgery. Patients' mean levels of fatigue were compared with normative data from a large sample of the general population. Furthermore, proportions of patients with (very) high fatigue scores were examined. Additionally, relationships of fatigue with sociodemographic, clinical and psychological variables were explored.

## METHODS

### Participants

Patients with histologically proven intracranial meningioma (WHO grade I), who underwent surgery between June 2014 and July 2017 at the Elisabeth-TweeSteden Hospital Tilburg, were included in this study. Patients were excluded if they had: multiple meningiomas; a history of intracranial neurosurgery or whole-brain radiation therapy; a history of severe psychiatric or neurological disease; a Karnofsky Performance Score (KPS) below 70; a lack of basic proficiency in Dutch; or severe motor, language or visual problems, limiting the ability to complete the assessments. Patients with severe surgery-related complications (e.g., stroke or meningitis) were excluded from the 12-month postoperative analyses.

### Procedure

Data of this study were prospectively collected as part of a larger follow-up study in patients with intracranial tumors who undergo resective surgery at the Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands. The study was approved by the Medical Ethics Committee Brabant (project number NL41351.008.12). Informed consent was obtained from all individual patients included in this study.

Neuropsychological assessments are administered one day before surgery (T0) and three months after surgery (T3; not used in the present analyses). These assessments have been embedded in standard clinical care for patients with intracranial tumors and

information from these assessments is also used in the multidisciplinary consultation that takes place every month. Three months after surgery, patients are invited by nurse practitioners to participate in a follow-up assessment (T12) for research purposes. Neuropsychological assessments consist of a standardized interview, questionnaires on anxiety, depression and cognitive complaints, and standardized neuropsychological tests (not included in the present analyses). Questionnaires on work, community integration and fatigue are administered at T0 and T12, but not at T3. All assessments were conducted in the hospital by well-trained test technicians.

This study focused on self-reported fatigue, which was examined one day before surgery (T0) and one year after surgery (T12). Because the pre- and postoperative questionnaires on fatigue were added to the existing test protocol simultaneously in June 2015, patients who participated in the one-year post surgery measurement between June 2015 and June 2016 (and had their preoperative assessment between June 2014 and June 2015), completed the MFI at T12, but did not fill out the preoperative questionnaire on fatigue.

### Study measures

**Fatigue.** Symptoms of fatigue were assessed using the Multidimensional Fatigue Inventory (MFI). Participants were asked to report their fatigue experiences over 'the last few days'. This 20-item questionnaire takes about five minutes to administer and covers the following five dimensions of fatigue: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. These scales are based on ways in which fatigue can be expressed, as indicated in the literature and as resulted from patient interviews.<sup>23</sup> Reliabilities of the five different scales are sufficient, with Cronbach's  $\alpha$  ranging from .72 to .87.<sup>23</sup> Questionnaires were not included if there were > 4 missing answers. In case of 1-4 missing items in less than 5% of the cases (Missing At Random or Missing Completely At Random), use was made of data imputation (using the mean of patient's filled out items on that particular scale). Representative normative data from the general population of Germany ( $n = 2037$ ) were available for comparison.<sup>24</sup> We used these norms to convert patients' raw scores into sex- and age-corrected Z-scores per subscale for both time-points. Higher Z-scores indicate greater fatigue severity. 'High' and 'very high' fatigue scores were determined by using widely-used cut-offs of, respectively, 1.3 (90<sup>th</sup> percentile) and 2.0 (97.5<sup>th</sup> percentile).<sup>25,26</sup>

**Anxiety and depressive symptoms.** The Hospital Anxiety and Depression Scale (HADS)<sup>27</sup>, originally developed for somatic outpatients, was used to assess symptoms of anxiety and depression. This widely-used screening instrument consists of 14 items, referring to symptoms within the last week, from which an anxiety scale score (HADS-A) and a depression scale score (HADS-D) can be derived. Higher scores indicate more psychological

distress. Reliability of the Dutch version of the HADS is satisfactory to good, with test-retest reliability coefficients between .86 and .90 and Cronbach's alphas ranging from .71 to .90.<sup>28</sup>

*Cognitive complaints.* The Cognitive Failures Questionnaire (CFQ)<sup>29</sup> was used to measure subjective cognitive functioning. Frequency of everyday cognitive failures in motor function, perception and memory was assessed with 25 items, with response options from 0 (never) to 4 (very often). Psychometric properties of the Dutch version of the CFQ were sufficient, with test-retest reliability of .83 and Cronbach's alphas of .75 and .81.<sup>30</sup>

*Sociodemographic and clinical variables.* Number of years of education and completed level of education were self-reported by the patients during a standardized interview. Education was classified using the Dutch coding system of Verhage<sup>31</sup>, which ranges from 1 (only primary school) to 7 (university degree). Its seven categories were subdivided into three levels, namely low (Verhage 1 to 4), middle (Verhage 5) and high educational level (Verhage 6 and 7). Relevant clinical information was extracted from electronic medical charts. The location of the tumor was classified by the neurosurgeon. Tumor volume was semi-automatically segmented by trained researchers using the software application ITK-SNAP.<sup>32</sup>

## Statistical analysis

Data are presented as means  $\pm$  standard deviations (SD) or frequencies and percentages. Preoperative and postoperative fatigue scores of the patient sample were compared to the normative sample using two-tailed one-sample z-tests. Two-tailed one-sample z-tests are conducted, since the means and SDs of the general population (i.e., normative sample) are known ( $M = 0$ ,  $SD = 1$ ). The standardized mean differences between patients and controls can be interpreted as effect sizes, with 0.20-.49 indicating small effects, 0.50-.79 medium effects, and  $\geq 0.80$  reflecting large effects.<sup>33</sup> Changes from preoperative to postoperative mean scores were examined using two-tailed paired-sample t-tests. Effect sizes were calculated by dividing the mean difference by its standard deviation (Cohen's  $d = M_{diff}/SD_{diff}$ ), again with 0.20-0.49 small, 0.50-0.79 medium, and  $\geq 0.80$  large effects.<sup>34</sup> Automatically, correlation coefficients between preoperative and postoperative levels of fatigue were calculated. Correlation coefficients of .10 to .29 were considered as small, .30 to .49 were considered as medium, and .50 to 1.0 reflected large correlation coefficients.<sup>34</sup>

The prevalence of high and very high fatigue levels was determined by counting individual patients who scored above the cut-offs of  $Z \geq 1.3$  (90<sup>th</sup> percentile) and  $Z \geq 2.0$  (97.5<sup>th</sup> percentile) respectively<sup>25,26</sup>, for each of the MFI subscales at each time-point.

To investigate clinical and demographic factors associated with dimensions of fatigue, correlation coefficients were calculated between the subscales of the MFI and sex, age, level of education, tumor hemisphere, preoperative tumor volume, use of AEDs, self-reported symptoms of anxiety/depression and self-reported cognitive complaints. Selected variables

were mainly based on previous studies in neuro-oncological patients<sup>7,15</sup>. Sex- and age-corrected fatigue scores were used<sup>24</sup>, but these variables were included in the correlation analysis as well, to check if there was no additional effect of sex and age in this patient sample. Pearson's product-moment correlations ( $r$ ) were calculated for the continuous variables, Spearman's rank-order correlations ( $\rho$ ) were applied to the ordinal variable (i.e. level of education) and point-biserial correlations ( $r_{pb}$ ) were used for the dichotomous variables. Interpretation of the correlation coefficients is described above. Statistical analyses were conducted using SPSS Statistics (version 24.0), with an alpha level of .05.

## RESULTS

### Patient characteristics

Data from preoperative assessments of 65 patients were included in this study (Table 1). Their mean age was  $56.2 \pm 12.1$  years and 74% were female. The majority of tumors were located in the frontal lobe (63%) and mean tumor volume was  $42.7 \pm 26.0$  cm<sup>3</sup>. At one-year post surgery, data from 53 patients were available of whom 34 also participated in the preoperative assessment. Data imputation was used in 4 cases with single missing values. Table 1 presents sociodemographic and clinical characteristics of the different groups.

**Table 1.** Sociodemographic, clinical and psychological characteristics of the different groups

Characteristic	Patients at T0	Patients at T12	Subgroup with both assessments
Sample size (n)	65	53	34
Age at T0 (Mean; SD)	56.2; 12.1	54.8; 11.3	54.2; 11.4
Sex (n female; %)	48; 74%	40; 76%	25; 74%
Years of education (Mean; SD)	14.4; 3.8	14.9; 3.5	14.9; 3.5
Level of education (n; %) <sup>a</sup>			
Low	17; 26%	12; 23%	8; 24%
Middle	24; 37%	10; 38%	15; 44%
High	24; 37%	21; 40%	11; 32%
Tumor hemisphere (n; %)			
Right	29; 45%	25; 47%	14; 41%
Left	26; 40%	20; 38%	15; 44%
Bilateral	10; 15%	8; 15%	5; 15%
Tumor location (n; %)			
Frontal	41; 63%	28; 53%	19; 56%
Non-frontal	16; 25%	18; 34%	10; 29%

Table 1. Continued

Characteristic	Patients at T0	Patients at T12	Subgroup with both assessments	
Posterior fossa	8; 12%	7; 13%	5; 15%	
Presenting neurological symptom (n; %) <sup>a</sup>				
Visual deficit	16; 25%	12; 23%	9; 26%	
Headache, dizziness	14; 22%	11; 21%	8; 24%	
Cognitive or language deficits	12; 18%	9; 17%	4; 12%	
Seizure	11; 17%	9; 17%	6; 18%	
Focal weakness	6; 9%	7; 13%	3; 9%	
Accidental finding	3; 5%	2; 4%	2; 6%	
Other	3; 5%	3; 6%	2; 6%	
Preoperative tumor volume (cm <sup>3</sup> ; Mean; SD) <sup>b</sup>	42.7; 26.0	41.7; 27.0	42.4; 25.7	
Use of antiepileptic drugs (n; %)	10; 15%	8; 15%	5; 15%	
Symptoms of anxiety (Mean; SD)	7.1; 4.5	4.0; 3.2	6.5; 4.0 <sup>c</sup>	3.6; 3.0 <sup>d</sup>
Symptoms of depression (Mean; SD)	6.1; 4.3	3.7; 3.6	5.3; 4.0 <sup>c</sup>	3.4; 3.7 <sup>d</sup>
Cognitive complaints (Mean; SD)	27.7; 13.0	33.3; 16.0	25.3; 12.5 <sup>c</sup>	32.4; 16.4 <sup>d</sup>

<sup>a</sup> Percentages may not add up, due to rounding.

<sup>b</sup> Data was available from 58 patients at T0 and 49 patients at T12.

<sup>c</sup> At T0

<sup>d</sup> At T12

### Mean levels of fatigue in patients with meningioma

Results of the group-level analyses are listed in Table 2. Patients' mean scores were significantly higher on each subscale of the MFI, both pre- and postoperatively, compared with norms from the general population (all *p*-values <.01). The largest effects were observed on the subscales of General Fatigue and Mental Fatigue, with effect sizes ranging from 0.89 to 1.07.

In the subset of patients who underwent both assessments (*n* = 34), improvements over time were observed for Reduced Activity and Reduced Motivation. No significant differences were observed between pre- and postoperative mean levels of General Fatigue, Physical Fatigue and Mental Fatigue (Table 3).

**Table 2.** Preoperative and postoperative mean patients' levels of fatigue compared to normative values

MFI Subscale	N	Mean <sup>a</sup>	SD	z-value	P-value	Effect size <sup>b</sup>
Preoperative fatigue (T0)						
General Fatigue	65	1.07	1.46	8.59	<.001*	1.07
Physical Fatigue	65	0.76	1.40	6.13	<.001*	0.76
Mental Fatigue	65	1.02	1.46	8.20	<.001*	1.02
Reduced Activity	65	0.88	1.24	7.12	<.001*	0.88
Reduced Motivation	65	0.77	1.40	6.18	<.001*	0.77
Postoperative fatigue (T12)						
General Fatigue	53	0.89	1.34	6.47	<.001*	0.89
Physical Fatigue	53	0.44	1.03	3.17	.002*	0.44
Mental Fatigue	53	1.07	1.38	7.82	<.001*	1.07
Reduced Activity	53	0.38	1.11	2.74	.006*	0.38
Reduced Motivation	53	0.36	1.16	2.64	.008*	0.36

<sup>a</sup> Higher scores indicate higher levels of fatigue. Test values (based on norms of Schwarz et al., 2003):  $m = 0$ ;  $s = 1$

<sup>b</sup> Standardized mean differences can be interpreted as effect sizes, with .20-.49 indicating small effects, .50-.79 medium effects, and  $\geq .80$  reflecting large effects.<sup>33</sup>

\*  $p < .05$

**Table 3.** Preoperative levels of fatigue compared to postoperative levels of fatigue in meningioma

T0-T12 pairs	N	Mean difference	SD <sub>diff</sub>	t-value	P-value	Effect size <sup>a</sup>	$r^b$
General Fatigue	34	0.09	1.67	0.31	.759	0.05	.37*
Physical Fatigue	34	0.40	1.40	1.68	.102	0.29	.39*
Mental Fatigue	34	0.23	1.44	0.94	.355	0.16	.48*
Reduced Activity	34	0.63	1.43	2.57	.015*	0.44	.25
Reduced Motivation	34	0.64	1.29	2.91	.006*	0.50	.45*

<sup>a</sup> Cohens  $d = M_{diff}/SD_{diff}$ , with .20-.49 indicating small effects, .50-.79 medium effects, and  $\geq .80$  reflecting large effects<sup>34</sup>

<sup>b</sup> Coefficients for correlations between pre- and post-surgery fatigue; coefficients of .10 to .29 were considered as small, .30 to .49 as medium, and .50 to 1.0 reflected large correlation coefficients<sup>34</sup>

\*  $p < .05$

### Prevalence and severity of fatigue in patients with meningioma

Figure 1 illustrates the proportions of patients scoring normal, high and very high per subscale of the MFI. Preoperatively, the prevalence of high fatigue (Z-score  $\geq 1.3$ ) varied between 34% for Reduced Motivation and 43% for General Fatigue and Mental Fatigue.

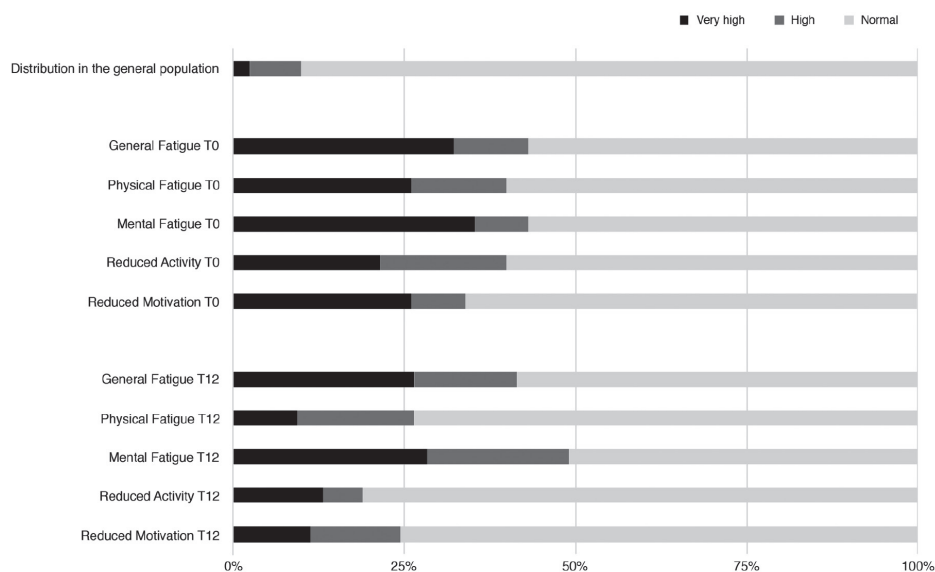


Postoperative prevalence of high fatigue ranged from 19% for Reduced Activity to 49% on Mental Fatigue.

In total, 44/65 patients (68%) scored high (Z-score  $\geq 1.3$ ) on one or more subscales of the MFI before surgery. Of these 44 patients, 35 scored very high (Z-score  $\geq 2.0$ ) on one or more subscales. Postoperatively, 30/53 patients (57%) scored high on one or more subscales and 21 of these patients scored very high on one or more subscales.

### Correlates of fatigue in patients with meningioma

As shown in Table 3, the preoperative fatigue scores were weakly to moderately correlated with fatigue scores at T12 ( $r$ 's between .25 and .48). Furthermore, correlation analyses showed medium to large associations between fatigue and self-reported symptoms of depression and cognitive complaints pre- and post-surgery, and with anxiety post-surgery (Table 4). We found no clear correlations between standardized scores on the subscales of the MFI and sex, age, education, tumor hemisphere, preoperative tumor volume and use of AEDs.



**Figure 1.** Prevalence of fatigue in patients with meningioma at T0 (n = 65) and T12 (n = 53)

Table 4. Correlates of fatigue in meningioma patients

	Preoperative assessment (T0) (n =65)					Postoperative assessment (T12) (n =53)				
	General Fatigue	Physical Fatigue	Mental Fatigue	Reduced Activity	Reduced Motivation	General Fatigue	Physical Fatigue	Mental Fatigue	Reduced Activity	Reduced Motivation
Sex	.02	.09	.04	-.02	.03	.20	.13	.07	.08	-.05
Age	-.24	-.23	-.15	-.11	.14	-.14	.08	-.19	.06	.10
Level of education	-.06	.03	-.12	-.11	-.15	.12	.08	.06	.15	.01
Tumor hemisphere <sup>a</sup>	.03	-.08	.02	.09	-.06	-.14	-.06	-.07	-.16	-.06
Preoperative tumor volume	.18	.20	.10	.20	.11	-.23	-.15	.06	-.29*	-.14
Use of AEDs	-.10	-.10	.00	.01	-.26*	.21	.27	.13	.26	.04
Anxiety	.17	.14	.16	.09	.36*	.39*	.37*	.49*	.31*	.44*
Depression	.44*	.47*	.38*	.49*	.65*	.58*	.61*	.59*	.59*	.56*
Cognitive complaints	.38*	.40*	.47*	.41*	.30*	.54*	.43*	.71*	.38*	.39*

Note: Correlations of .10 to .29 were considered as small, .30 to .49 as medium, and .50 to 1.0 reflected large correlation coefficients.<sup>34</sup> Correlations > .29 in bold.

<sup>a</sup> Patients with bilateral tumors were not included in these analyses

\*  $p < .05$

## DISCUSSION

In this study we comprehensively examined pre- and postsurgical prevalence, severity and correlates of fatigue in patients with meningioma using a multidimensional fatigue instrument. Symptoms of fatigue were assessed in patients with WHO grade I meningioma prior to surgery ( $n = 65$ ) and one year after surgery ( $n = 53$ ). On all subscales of the MFI, patients reported more fatigue compared to norms of the general population, both before and one year after surgery. In total, 68% and 57% of the patients scored (very) high on one or more subscales of the MFI before and after surgery respectively. In general, proportions of patients scoring very high were larger than proportions of patients scoring high, indicating that the reported symptoms were rather severe than mild. Furthermore, mean levels of General Fatigue, Physical Fatigue and Mental Fatigue did not decrease significantly over the one-year follow-up period in a subgroup of patients ( $n = 34$ ). These findings indicate that fatigue is a substantial and persistent clinical problem in meningioma patients up to one year after surgery.

The prevalence rates found in this study roughly correspond with those found in patients with glioma.<sup>7,8,14</sup> This may seem remarkable given the differences in etiology and oncological prognosis between meningioma and glioma. Glioma infiltrate the brain and are the leading cause of death in patients due to disease progression. Meningioma, on the other hand, grow extra-axially and are mostly benign.<sup>1</sup> However, previous studies have also demonstrated long-term impairments in cognitive functioning and quality of life in patients with meningioma.<sup>4,5</sup> Although it is often assumed that meningioma patients recover well after surgery, this research contributes to the finding that a substantial number of patients are left with various problems, even long after medical treatment has ended.

Our results indicate that patients' motivation and activity were significantly increased one year after surgery, but serious fatigue remained present in their daily functioning. Persistent symptoms of fatigue can lead to several problems, including difficulties in social participation, mental health issues or inability to return to (previous) work.<sup>35</sup> Fatigue may not only affect patients' lives, but also the lives of their families.<sup>35</sup> However, results of the within-group analyses must be interpreted with some caution, since only a part of the participants completed both the preoperative and postoperative questionnaires ( $n = 34$ ). Furthermore, although stability is observed at group level on three subscales of the MFI, it is possible that different patterns of change occur on the individual level.<sup>36</sup> An interesting next step would be to look at individual-level change in fatigue scores (compared to change scores of an appropriate control group) and predictors of improvement or decline using a longitudinal study design with more patients.

In the present sample, fatigue was associated with self-reported symptoms of depression, anxiety and cognitive complaints. These findings correspond with previous observations in patients with glioma<sup>7,8,17,37</sup>, as well as with findings in other patient populations.<sup>38-40</sup> Due

to interconnectedness and overlap of symptoms, it is difficult to distinguish between, for example, a major depressive disorder and serious fatigue. Depression can cause fatigue and vice versa, and a third factor can cause both depression and fatigue. It is possible that these symptoms are an expression of shared neurobiological mechanisms (e.g., inflammation or brain abnormalities), but these mechanisms have not been extensively studied in patients with meningioma yet. Furthermore, sleep-wake disturbances are common in brain tumor patients<sup>41,42</sup>, and often co-occur with symptoms of fatigue, depression and anxiety, but for this study, we did not collect data on sleep quality. More extensive research is necessary to gain insight into causal relationships between fatigue and its multifactorial determinants in patients with meningioma.

In this study, the highest prevalence rates were found for Mental Fatigue. Short unidimensional questionnaires or subscales used in previous research often contain floor and ceiling effects due to the narrow range of possible scores and moreover, tend to measure mainly symptoms of physical fatigue.<sup>43</sup> To prevent problems with (mental) fatigue being under-diagnosed and thus under-treated, we recommend the use of a short validated multidimensional screening tool, such as the MFI, for patients with surgically treated meningioma during aftercare. Ideally, for each patient with increased scores, contributing and perpetuating factors should be identified using a comprehensive examination. By addressing these specific factors, treatment can be better tailored to the individual patient.<sup>44</sup> Although only a few intervention studies have been done on fatigue in patients with brain tumors, there is some evidence that patients who experience fatigue may benefit from exercise interventions or psychological interventions (e.g., cognitive behavioral therapy or educational programs) to help patients manage symptoms of fatigue.<sup>41,45-48</sup> Treatment with psychostimulants have been shown to have insufficient effect on symptoms of fatigue in patients with brain tumors.<sup>49,50</sup>

This study has some limitations that should be attended to in further studies. The sample sizes were relatively small, and only a subset of patients completed both the preoperative questionnaire and the one-year follow-up assessment. There are other factors that may have affected generalizability. For example, we included participants who underwent surgery and who had relatively favorable clinical characteristics (e.g., patients without a history of neurological/psychiatric disorders, with a KPS above 70 and without surgery-related complications). This could have resulted in an underestimation of fatigue in patients with meningioma in general. It is also possible that the timing of the first assessment (i.e., one day before surgery) may have influenced the results, since psychological distress appeared to be related to self-reported fatigue.

The current study is a necessary first step in investigating fatigue in patients with meningioma, but clearly more work has to be done in this area. The relationship between fatigue, sleep quality, medication use, and objective measures of cognitive functioning

should be further clarified. At the same time, research on treatment options for fatigue in patients with brain tumors should be expanded.<sup>45</sup>

The findings of the current study indicate that fatigue is a serious, common and persistent symptom in patients with meningioma undergoing neurosurgery. Health care providers and researchers should be aware of this, pay attention to this debilitating symptom and provide appropriate care.

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PART II

# COGNITIVE REHABILITATION





## CHAPTER 5

# Feasibility of the evidence-based cognitive telerehabilitation program *ReMind* for patients with primary brain tumors



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## ABSTRACT

Many patients with primary brain tumors experience cognitive deficits. Cognitive rehabilitation programs focus on alleviating these deficits, but availability of such programs is limited. Our large randomized controlled trial (RCT) demonstrated positive effects of the cognitive rehabilitation program developed by our group. We converted the program into the iPad-based cognitive rehabilitation program *ReMind*, to increase its accessibility. The app incorporates psychoeducation, strategy training and retraining. This pilot study in patients with primary brain tumors evaluates the feasibility of the use of the *ReMind*-app in a clinical (research) setting in terms of accrual, attrition, adherence and patient satisfaction. The intervention commenced 3 months after resective surgery and patients were advised to spend 3 h per week on the program for 10 weeks. Of 28 eligible patients, 15 patients with presumed low-grade glioma or meningioma provided informed consent. Most important reason for decline was that patients (7) experienced no cognitive complaints. Participants completed on average 71% of the strategy training and 76% of the retraining. Some patients evaluated the retraining as too easy. Overall, 85% of the patients evaluated the intervention as “good” or “excellent”. All patients indicated that they would recommend the program to other patients with brain tumors. The *ReMind*-app is the first evidence-based cognitive telerehabilitation program for adult patients with brain tumors and this pilot study suggests that postoperative cognitive rehabilitation via this app is feasible. Based on patients’ feedback, we have expanded the retraining with more difficult exercises. We will evaluate the efficacy of *ReMind* in an RCT.

## INTRODUCTION

Many patients with primary brain tumors suffer from cognitive deficits.<sup>1,2</sup> These deficits can cause difficulties in patients' everyday lives and affect their quality of life.<sup>3,4</sup> Reported prevalence rates of cognitive deficits vary widely, which is partly due to the differences in used methods, but range between 19% and 90%.<sup>2,5,6</sup> Since survival rates are increasing<sup>7,8</sup> and patients are living longer with possible cognitive deficits, management of cognitive deficits becomes an increasingly important part of total care in patients with primary brain tumors.

Unfortunately, treatment options for these cognitive deficits are scarce. Over the last years, a few intervention studies have been conducted in brain tumor patients, which demonstrated positive effects of cognitive rehabilitation.<sup>9-11</sup> Our randomized controlled trial (RCT) in 140 glioma patients with stable disease demonstrated positive effects of a 6 weeks' face-to-face cognitive rehabilitation program that consisted of psychoeducation, teaching of use of compensatory skills and retraining.<sup>9,12</sup> Despite the positive findings of previous studies and patients' needs for rehabilitation services, cognitive rehabilitation is not always accessible for every patient in clinical practice.<sup>13,14</sup> Conventional in-person cognitive rehabilitation can be demanding and costly, due to, amongst others, multiple hospital visits and lengthy face-to-face sessions with professionals.

To overcome some of the limitations of conventional cognitive rehabilitation, a number of studies explored the possibilities of cognitive telerehabilitation programs in other neurological and oncological patient populations.<sup>15-18</sup> Cognitive telerehabilitation is a form of eHealth, and it is defined as "the use of information and communication technologies to provide rehabilitation services to people remotely in their homes or other environments".<sup>19</sup> To our knowledge, no studies on cognitive telerehabilitation have been conducted in adult patients with brain tumors.

Based on the positive findings of our previous RCT, and ongoing requests of doctors and patients to utilize the cognitive rehabilitation program, we converted our program into an iPad-based cognitive rehabilitation application, named *ReMind*. The goal of the development of the *ReMind*-app was to increase the accessibility of the program to brain tumor patients in a cost-efficient mode of delivery, while maintaining the contents of the original program. Before we initiated an RCT to evaluate the efficacy of *ReMind*, we conducted a small-scale study to investigate the feasibility of, and potential barriers to, the use of the program in the clinical (research) setting in terms of accrual, attrition, adherence and patient satisfaction. Since cognitive telerehabilitation has not yet been investigated in adult patients with primary brain tumors (i.e. vulnerable patients with higher levels of fatigue, psychological distress and concentration problems), this feasibility study is an important first step.

## METHODS

### Participants

Patients with a radiologically suspected supratentorial low-grade glioma or meningioma, who were scheduled for resective surgery in the Elisabeth-TweeSteden Hospital Tilburg, were invited to participate. Patients who met any of the following criteria were excluded: history of intracranial neurosurgery, history of severe psychiatric or neurological disorder, diagnosis of multiple meningioma, complete unfamiliarity with the use of computers, lack of basic proficiency in Dutch, inability to undergo neuropsychological assessment due to motor/language/visual problems, Karnofsky Performance Score (KPS) below 70 or a premorbid IQ below 85. Patients who were referred to in- or outpatient cognitive rehabilitation were excluded as well. The projected sample size was 15. Informed consent was obtained from all individual participants included in the study.

### Design and procedure

This single-arm pilot study was approved by the local medical ethical review board (METC Brabant: NL51152.028.14), registered in The Netherlands National Trial Register (NTR 5392).

Two weeks before surgery, patients were informed about the study by a nurse practitioner. Interested patients received an information letter. One day before surgery, patients were hospitalized and neuropsychological assessment (T0) was carried out as part of usual clinical care. At the beginning of the assessment, patients who were willing to participate in the study provided written informed consent. If patients chose to make use of the possibility to involve a significant other in the cognitive rehabilitation trajectory (see below), the significant other had to give informed consent as well. Three months after surgery, a second usual care neuropsychological assessment (T3) was conducted. Immediately afterwards, the cognitive telerehabilitation program *ReMind* commenced. Three months later (i.e. six months after surgery), after completing *ReMind*, the final neuropsychological assessment took place (T6) for the purpose of this study. Additionally, study-specific evaluation questionnaires were completed. The current study was embedded in standard clinical care provided by the hospital.

### Intervention

*The program.* The cognitive telerehabilitation program *Remind* was developed in a joint patient/researcher initiative and is based on our previously evaluated face-to-face cognitive rehabilitation program.<sup>9,12,20</sup> The *ReMind*-app is provided via an iPad (Figure 1(a)) and is available in both Dutch and English. In the current study, the Dutch version was used.

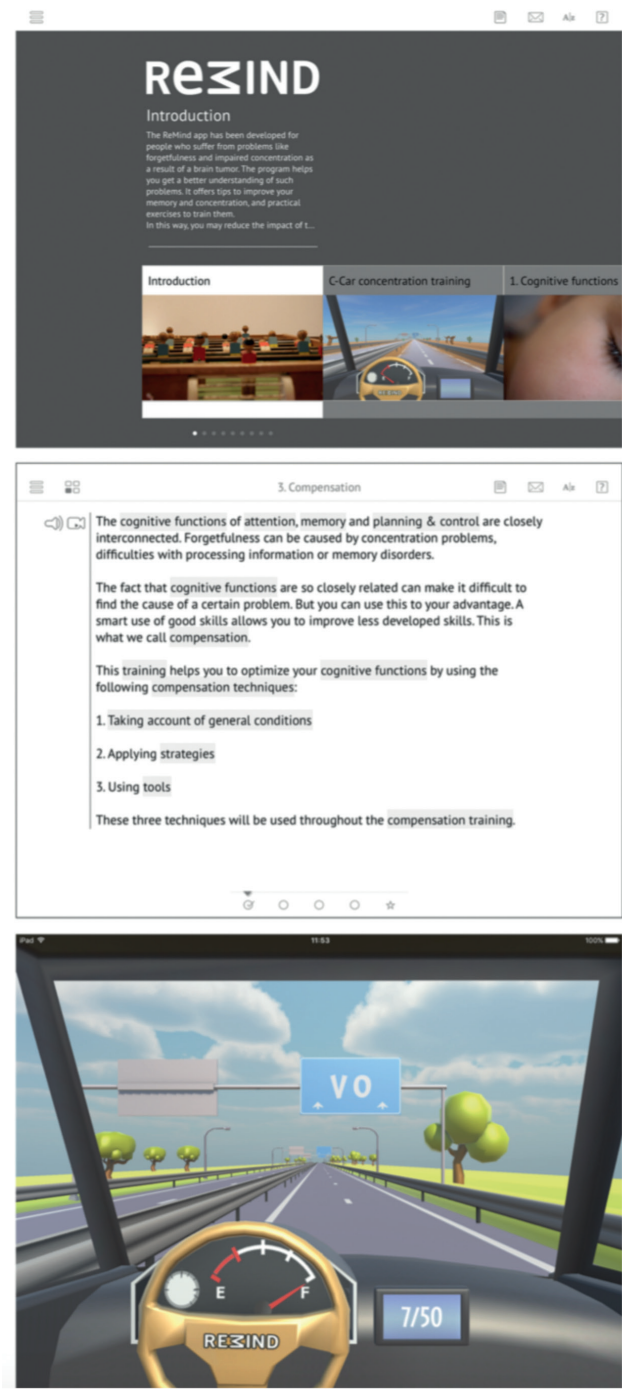
Similar to the original program<sup>12</sup>, *ReMind* consists of compensation training, including psychoeducation and teaching of compensatory skills, and attention retraining (see Figure 1(b) and 1(c)). In the compensation training, psychoeducation about cognitive functions is provided in six modules, namely on 1) Cognitive functions, 2) Influences, 3) Compensation, 4) Attention, 5) Planning & control, and 6) Memory. Additionally, in each module, compensatory strategies are taught and many exercises are included to learn to apply these strategies in everyday life. Patients learn, for example, to minimize distraction and deal with time pressure, and to optimally use external devices for support. Due to the strong interdependence of all cognitive functions, the strategy training was designed so that patients should go through all the 6 modules one by one, to benefit the most from the strategy training. Progression through each module is visualized, with checkmarks at the bottom of the screen (Figure 1(b)).

In the retraining part, named *C-Car*, four different modes of attention are trained, namely sustained, selective, alternating and divided attention. It includes visual and auditory exercises, wherein both verbal and numeric stimuli are presented. All patients started with the same version of this training, independently of their pre-intervention neuropsychological scores. Series of hierarchically graded tasks were used, so that higher levels are reached, if previous levels are mastered. In this manner, the retraining is tailored to the level of the patient. After each exercise, patients receive feedback on their performance.

During the development of the app, optimum use was made of the additional (technical) possibilities the new environment offered. The instructional texts of the strategy training are provided in videos, audio clips and read-only formats and patients can look back as often as they feel necessary. *ReMind* incorporates several other functions to make it as user-friendly as possible, such as help-overlay screens and links to explanations of important definitions. The program also offers the possibility to involve a significant other, which can be a spouse, family member, friend or professional: the *ReMinder*. Patients can send this *ReMinder* an email from anywhere in the program, for example to ask for advice when they get stuck in a text or an exercise.

**Guidance.** Three months after surgery, immediately after the second neuropsychological assessment (T3), a face-to-face appointment was planned, to hand over the iPad on which the *ReMind*-app was installed together with an explanation of the app. During the intervention period, the researcher contacted the patients by telephone every two weeks, to check on their progress, plan the course of their training and to address questions. It was advised and expected that patients spent 3 hours per week on the program, to complete the program within 10 weeks. A second face-to-face appointment took place at the end of the program, to retrieve the iPad and to collect the completed questionnaires.





**Figure 1.** Screenshots of different parts of *ReMind*: **a** homepage, **b** strategy training, and **c** retraining

## Measures

*Accrual and attrition.* Accrual was defined as the total number of included patients as compared to the number of invited patients. The number of patients who declined participation and reasons for decline were carefully recorded. The same was done for the number of patients who dropped out of the study and reason(s) for this attrition.

*Adherence.* Adherence to the program was indicated by both the number of completed module sections in the strategy training and the number of exercises performed in the retraining, each expressed in percentages of total available sections and exercises, respectively. If patients completed  $\geq 80\%$  of both the strategy training and the retraining, adherence was considered acceptable. To calculate mean percentages for the group, a maximum of 100% per individual was used, even if patients worked through the program more than once. Reasons for non-adherence as reported in the telephone calls during the intervention and in the face-to-face appointment at the end of the program were recorded.

*Patient experience.* After completing the program, patients were requested to fill out a study-specific questionnaire, evaluating their experiences with *ReMind* (e.g., satisfaction, enjoyment, usefulness and burden), whether they would recommend any changes in (elements of) the program, and if they would recommend it to other patients.

*Feasibility of neuropsychological assessments.* Neuropsychological tests and patient-reported outcome measures (PROMs) were administered to describe baseline functioning of the patients and to test the feasibility of procedures for later use on a larger scale. Objective cognitive functioning was assessed by the computerized neuropsychological test battery CNS Vital Signs<sup>21,22</sup> and three paper-and-pencil tests, namely Letter Fluency, Digit Span (WAIS), and Paired Associates (WMS).<sup>23-25</sup> Z-scores were calculated using normative data and Z-scores  $\leq -1.5$  were considered as low. Subjective cognitive functioning was assessed with the Cognitive Failures Questionnaire (CFQ).<sup>26</sup> Based on Dutch representative normative data<sup>27</sup>, a total score of  $\geq 42$  was considered as clinically high. Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS)<sup>28,29</sup>, with a cut-off for both scales of  $\geq 8$ .

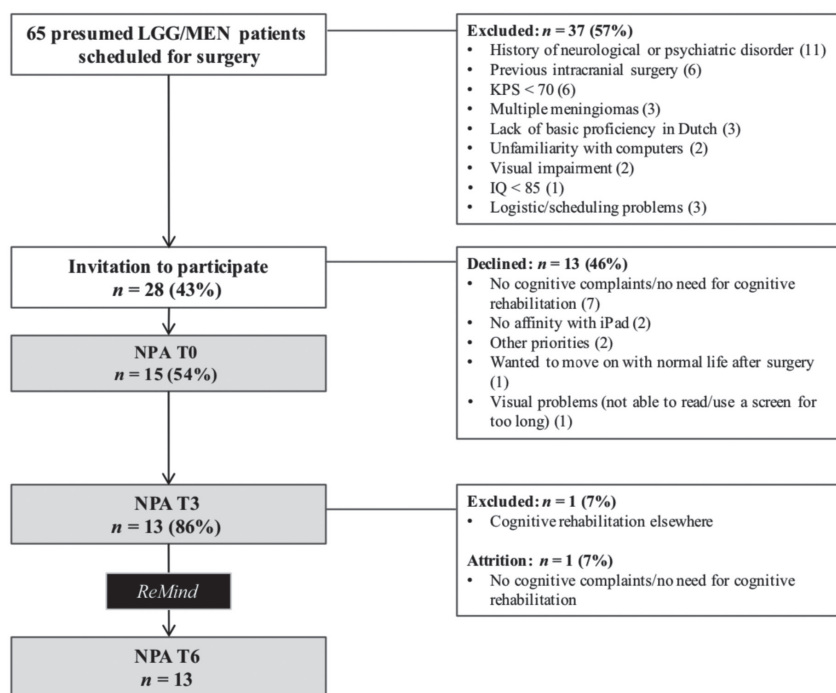
## Data analysis

Percentages of eligible, included, excluded and dropped-out patients were calculated. Descriptive statistics of participants are presented. This feasibility study ( $n = 15$ ) was not designed, and therefore not powered, to evaluate the efficacy of *ReMind*.

## RESULTS

### Accrual and attrition

Data on accrual and attrition are presented in a flow diagram (Figure 2). Out of 65 consecutive patients who were scheduled to undergo surgery for presumed low-grade glioma/meningioma, 37 patients (57%) were excluded. Of the 28 eligible patients who were invited to participate, 15 patients provided informed consent (54%) and 13 patients (46%) declined. The most important reason for decline was that patients ( $n = 7$ ) did not experience cognitive deficits and felt no need to follow a cognitive rehabilitation program at this stage. In the 3 months prior to the start of the intervention, one patient withdrew from the study because of lack of cognitive complaints. An additional patient was excluded after informed consent, since she was referred to cognitive rehabilitation elsewhere. No dropout occurred during the intervention phase. Nine participants (69%) chose to involve a significant other (in all cases, a spouse).



**Figure 2.** Flowchart of enrolment and attrition.

NPA neuropsychological assessment, LGG low-grade glioma, MEN meningioma, KPS Karnofsky performance score

Table 1. Characteristics and adherence per participant

	Sex	Age	Education (Years; Level <sup>a</sup> )	Histology	Tumor hemisphere	Tumor location	RTx	CTx	AED	OCF <sup>b</sup> at T3	PROM <sup>c</sup> at T3	Significant other involved	Strategy training completed (%) <sup>d</sup>	Retraining completed (%) <sup>d</sup>	Reported difficulties <sup>e</sup>
1	♂	68	17; 6	MEN	Left	Frontal	No	No	No	2	No	Yes	83	100	A
2	♀	54	15; 6	MEN	Bilateral	Frontal	No	No	No	0	No	No	62	178	A
3	♂	53	18; 6	MEN	Right	Temporal	No	No	Yes	0	No	No	100	56	B/C
4	♀	43	15; 6	MEN	Right	Frontal	No	No	No	1	No	No	17	15	D
5	♂	54	15; 5	Inconcl.	Right	Parieto- occipital	No	No	Yes	4	An+D	Yes	100	81	
6	♂	59	13; 5	GBM	Right	Insular	Yes	TMZ	Yes	0	No	Yes	42	100	
7	♂	44	16; 6	LGG <sup>f</sup>	Left	Temporal + Insular	Yes	No <sup>g</sup>	No	1	No	Yes	100	131	
8	♂	61	16; 6	LGG <sup>f</sup>	Right	Frontal	Yes	TMZ	Yes	5	D	Yes	83	84	E/F
9	♀	43	13; 4	MEN	Bilateral	Frontal	No	No	Yes	3	No	No	17	13	E
10	♂	56	17; 6	MEN-II	Right	Frontal	Yes	No	Yes	0	No	Yes	100	100	E
11	♂	40	20; 6	LGG <sup>f</sup>	Left	Temporal	Yes	TMZ	Yes	0	No	Yes	100	103	
12	♀	52	14; 5	MEN	Bilateral	Frontal	No	No	No	0	No	Yes	17	31	D
13	♀	47	18; 6	LGG	Right	Frontal	No	No	Yes	1	D	Yes	100	100	
<b>Total</b>	♂:8 ♀:5	Mean 52 Median 52	Mean 16 Median 16	MEN: 7 LGG:4	L: 3   R: 7 Bi: 3	Frontal: 8 62%	5 38%	3 23%	8 62%	7 54%	3 23%	9 69%	Mean (median) 71 (83)	Mean (median) 76 (100)	

RTx radiotherapy prior or during ReMind, CTx chemotherapy prior or during ReMind, AED anti-epileptic drugs, OCF objective cognitive functioning, PROM patient-reported outcome measure, MEN meningioma (WHO-grade I), MEN-II WHO-grade II meningioma, LGG low-grade glioma, GBM glioblastoma multiforme, TMZ temozolomide, An = anxiety, D = depression

**Table 1.** Continued

<sup>a</sup> Education is classified according to the Dutch coding system of Verhage ranging from 1 (less than primary education) to 7 (university degree) (Verhage, 1964)

<sup>b</sup> Number of impaired outcomes of objective cognitive functioning (Z-score of  $\leq -1.5$ ; 11 scores were considered)

<sup>c</sup> PROMs included the CFQ and HADS, with cut-offs of  $\geq 42$  and  $\geq 8$  respectively, 'No' indicated no scores above the cut-offs

<sup>d</sup> Adherence rates  $\geq 80\%$  were considered as acceptable. To calculate mean percentages, a maximum of 100% per individual was used

<sup>e</sup> A: illness of spouse, B: technical problems, C: return to full-time work, D: rehousing, E: severe fatigue due to adjuvant treatment

<sup>f</sup> Awake craniotomy

<sup>g</sup> Received temozolomide after T6

### Demographic, clinical and neuropsychological characteristics

Table 1 shows the demographic, clinical and neuropsychological characteristics of the sample. Thirteen patients (38% female), with a mean age of 52 years (range 40 – 68), followed the cognitive rehabilitation program and completed all assessments. Six patients were diagnosed with a grade I meningioma, one patient with a WHO grade II meningioma and four patients with a WHO grade II glioma. For two other patients, the radiologically suspected diagnosis of low-grade glioma was not confirmed after surgery (Table 1). After surgery, five patients (38%) were treated with radiotherapy and three of these patients also received chemotherapy at T3. The majority (69%) of the patients were highly educated. Before the start of the intervention, seven patients demonstrated low Z-scores ( $\leq -1.5$ ) on one or more measures of objective cognitive functioning. Based on the scores of the HADS, three of the patients possibly suffered from depression, and one of them possibly from anxiety as well (Table 1).

### Adherence

Adherence per participant is presented in Table 1. On average, participants completed 71% of the strategy training 76% of the retraining. According to our definition of adherence (completion of  $\geq 80\%$  of both the strategy training and the retraining), seven out of 13 patients (54%) adhered to the program. Six patients (46%) completed the entire strategy training and seven patients (54%) completed the entire retraining. Four patients (31%) fully completed both the strategy- and retraining. Three participants reported specific circumstances that explained non-adherence: one was confronted with serious illness of her spouse, one experienced technical problems with the retraining part of the program (which were solved afterwards) and one moved to a new house during the intervention. Two participants who had a (very) low adherence to the program reported that they were too busy with other activities and had other priorities. On the other hand, other patients also experienced interfering circumstances, but were still able to adhere to the intervention.

One low-grade glioma patient reported that following the program was burdensome in combination with adjuvant tumor treatment.

### Patient experience

Results of the study-specific evaluation questionnaire are listed in Table 2. The majority evaluated the difficulty and the quantity of psychoeducation, fill-in exercises (to practice with learned strategies) and retraining tasks as sufficient. However, four participants reported that there were too many fill-in exercises included in the strategy training, whereas four other participants rated the retraining as (a bit too) easy and found there were (too) few retraining exercises included in the program. Furthermore, eight patients enjoyed working with *ReMind*. Using an iPad-app for cognitive rehabilitation was appreciated. Overall, 11 patients (85%) evaluated the cognitive rehabilitation program *ReMind* as “good” or “excellent”. All participants indicated that they would recommend the program to other brain tumor patients.

### Feasibility of neuropsychological assessments

Three patients were excluded from the study beforehand, because they did not undergo the first neuropsychological assessment (T0) due to (logistical) problems with planning. All 13 participants fully completed neuropsychological assessments, one questionnaire of a participant was not returned.

**Table 2.** Post-intervention ratings of different aspects of *ReMind* (n = 13)

Difficulty of	(too) easy	just right	(too) difficult
Information in strategy training	3	10	-
Fill-in exercises in strategy training	1	10	2
Retraining (C-Car game)	4	9	-
Amount/number of	(too) little/few	about right	(too) much/many
Information in strategy training	1	12	-
Fill-in exercises in strategy training	-	9	4
Retraining exercises (C-Car game)	4	8	1
Supervision of the researcher/trainer	-	13	-
Usefulness of	(very) useful	neutral	not (very) useful
Information in strategy training	7	6	-
Fill-in exercises in strategy training	3	9	1
Retraining exercises (C-Car game)	11	2	-
(telephone) contact with the researcher/ trainer	13	-	-

**Table 2.** Continued

Content addressed daily problems	<b>fully/largely</b>	<b>partly</b>	<b>not</b>
	8	4	1
Application of learnt (strategies) in daily life	<b>often/regularly</b>	<b>sometimes</b>	<b>seldom/never</b>
	3	5	5
Impact of cognitive problems has changed	<b>yes, positively</b>	<b>no<sup>a</sup></b>	<b>yes, negatively</b>
	6	7	-
Coping with cognitive problems has changed	<b>improved coping</b>	<b>no<sup>b</sup></b>	<b>worsened coping</b>
	5	8	-
Pleasantness of working on <i>ReMind</i>	<b>(very) pleasant</b>	<b>neutral</b>	<b>(very) unpleasant</b>
	8	3	2
	<b>excellent/good</b>	<b>sufficient</b>	<b>insufficient/poor</b>
Using an iPad-app for cognitive rehabilitation	11	1	1
Capability of the researcher/trainer	13	-	-
Contact with the researcher/trainer	12	1	-
Overall rating of the program	11	1	1
	<b>yes</b>	<b>no</b>	
Recommendation to other brain tumor patients	13	0	

<sup>a</sup> No change, there was no impact on daily life (5) or no change, impact remained the same (2)

<sup>b</sup> Coping is still good (8), or coping is still not good (0)

## DISCUSSION

*ReMind* is the first cognitive telerehabilitation program specifically developed for adult patients with primary brain tumors. The current pilot study was designed to test the feasibility of an evidence-based telerehabilitation program in the clinical (research) setting in preparation for a larger RCT. The results suggest that, for the subset of interested patients who were included in the study based on specific criteria, cognitive rehabilitation by using the *ReMind*-app was feasible. Overall, participants were satisfied with the program and dropout was low.

The recruitment of participants to the study was the most challenging aspect of this feasibility study. A substantial part (57%) of the patients who were undergoing surgery for low-grade glioma or meningioma were not eligible based on the exclusion criteria. In

hindsight, the exclusion criteria appeared to be overly strict, which, in an attempt to reduce bias through controlling patients' characteristics and potential confounders, potentially compromised the generalizability of the results to the target patient population of patients with presumed low-grade glioma and meningioma.<sup>30,31</sup> In particular, a large proportion of patients with a history of neurological/psychiatric disorders or previous intracranial surgery were excluded, although cognitive rehabilitation may be relevant for them as well. Based on these experiences, we adapted the inclusion criteria of the RCT. Furthermore, 46% of eligible patients declined participation, half of them reporting to feel no need to undergo cognitive rehabilitation at this stage ( $n = 7$ ). Two patients specifically declined participation since an iPad-based intervention was not appealing to them.

With respect to adherence, 54% of the participants met the criterion for sufficient (completion of  $\geq 80\%$  of both the strategy training and the retraining) adherence, which was comparable with other studies that investigated psychological eHealth interventions in other patient populations<sup>32</sup>, but not as high as the adherence to the face-to-face program in our previous RCT.<sup>9,12</sup> Whereas our previous study included a sample of patients with clinically stable lower-grade gliomas with a disease duration of several years, the patients in the present study participated only shortly after, or even during, the tumor treatment phase of their disease. For example, five patients received adjuvant treatment during the intervention. The patients in our pilot study lived through a turbulent period, in which psychosocial developments, in addition to medical treatment and recovery, are predominating. Some of them resume their work and/or family care during this period. It may be that, for some patients, undergoing cognitive rehabilitation in this phase is (too) burdensome. Furthermore, in contrast to our previous study, experiencing subjective cognitive (or objective) dysfunction was not an inclusion criterion. Consequently, not all patients in our sample experienced cognitive dysfunction (yet), which may have led to a lack of motivation to fully adhere to the program for some. Along this line, all three participants who reported psychological complaints showed (more than) sufficient adherence rates.

In order to reduce the well-known problems with adherence in remote interventions and, in particular, to find substitutes for the low amount of (face-to-face) supervision, before the start of the pilot study, we incorporated several features into the program that are known to enhance adherence.<sup>32-34</sup> For example, we provided regular guidance during the intervention, through telephone counseling and by provision of feedback from the program itself. Additionally, the program offers the possibility to patients to involve a significant other in the process, an option that nine patients chose. Seven of these patients showed sufficient adherence rates. Despite the efforts made, adherence rates were suboptimal.

Overall, participants who followed the program reported that an iPad-app was an appropriate mode of delivery of cognitive rehabilitation. In fact, this mode enables many patients with brain tumors to follow a cognitive rehabilitation program at their own homes,



which is a great advantage since many patients are not allowed to drive due to epileptic seizures. Another important advantage is that patients can follow the program at their own pace and can spread the material over as many sessions as they want, which could be helpful for (vulnerable and/or) older patients in particular.<sup>20</sup> All patients indicated that they would recommend the program to other brain tumor patients. However, some participants indicated that the retraining was too easy for them. Therefore, we decided to expand the retraining with nine more difficult exercises for use in the RCT and beyond, ensuring that the retraining remains challenging for each individual.

In intervention studies, the timing of the intervention is an important, but difficult issue, wherein a balance is sought between intervening not too early, but also not too late. Research in patients with brain tumors demonstrated that the need for supportive care is very high, especially in the early stage of the disease.<sup>14</sup> We hypothesized that early cognitive rehabilitation may enhance the recovery process and may prevent/minimize the negative impact of cognitive side effects of adjuvant treatment, and we decided to start the intervention soon after physical recovery from the surgery and after completion of radiotherapy. At three months after surgery, the intervention could be easily embedded in the existing logistics of our clinical aftercare, thereby minimizing patient burden. Because of the hypothesized preventative effects at this stage, both patients with and without cognitive complaints/deficits were eligible. We assume that several aspects of our cognitive rehabilitation program, for example psychoeducation about cognitive (dys)functioning in patients with brain tumors, could be helpful for a broad group of patients at an early stage.

We have started a larger trial to evaluate the efficacy of *ReMind* with respect to cognitive functioning and patient-reported outcomes, in which patients are consecutively randomized to an intervention group or waiting-list control group by minimization<sup>35</sup> after the 3 months' assessment. Based on the experiences in the pilot study, exclusion criteria were revised to include a broader group of patients and two participating medical centers were added. A 6-months follow-up assessment was added to the design and participants are requested to keep records of their time spent on the program using registration forms. In addition, a pilot study in 20 glioma patients with stable disease and cognitive complaints is currently being conducted, using the English version of the *ReMind*-app, at the University of California, San Francisco (UCSF) (clinicaltrials.gov NCT02783495). Ultimately, if the results of the RCT demonstrate beneficial effects of *ReMind* at the postoperative stage, this telerehabilitation program may enable many patients with brain tumors to follow a cognitive rehabilitation program at their own pace in their own environment early in the course of the disease.

## **ACKNOWLEDGEMENTS**

We would like to thank Sophie Rijnen, Astrid de Munnik, Lieke van den Heuvel, Febe Slikboer and Eileen Kessel for their contribution to the data collection.

## **Conflict of interest statement**

The authors declare that there is no conflict of interest.

## **Funding**

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## CHAPTER 6

# Study protocol for a randomized controlled trial evaluating the efficacy of an evidence-based app for cognitive rehabilitation in patients with primary brain tumours



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## ABSTRACT

**Background:** Many patients with primary brain tumors suffer from cognitive deficits, which negatively impact their quality of life. However, cognitive rehabilitation programs for these patients are scarce. We developed an iPad-based cognitive rehabilitation program for brain tumor patients, which was based on our effective face-to-face cognitive rehabilitation program. After successful completion of a feasibility study, a randomized controlled trial (RCT) has been started.

**Objective:** The aim of the RCT is to evaluate the immediate and longer-term effects of the iPad-based program on cognitive performance and patient-reported outcome measures (PROMs) in patients with primary brain tumors in an early stage of the disease.

**Methods:** Prior to surgery, patients with presumed low-grade glioma and meningioma are included. Before surgery and three months after surgery, neuropsychological assessments are conducted. After the second neuropsychological assessment, patients are assigned to the intervention group or waiting-list control group. The intervention consists of psychoeducation, compensation training and retraining. Patients are advised to spend 3 h per week on the program for 10 wk. Immediately after completion of the program and a half-year thereafter, post-intervention assessments take place. Patients in the control group are offered the opportunity to follow the program after all study assessments.

**Expected outcomes:** We expect that early cognitive rehabilitation has beneficial effects on cognitive performance and PROMs in brain tumor patients.

**Discussion:** The iPad-based program allows brain tumor patients to follow a cognitive rehabilitation program from their homes. Forthcoming results may contribute to further improvement of supportive care for brain tumor patients.

## GENERAL INFORMATION

### Protocol Title

Cognitive rehabilitation in brain tumor patients after neurosurgery.

### Trial Registration

The study has been registered in The Netherlands National Trial Register (NTR 5392) and on ClinicalTrials.gov (NCT03373487).

### Funding

This research (project number: 842003009) is supported by the Dutch organization for health research and innovation, ZonMw (Laan van Nieuw Oost-Indie 334, 2593 CE, The Hague, The Netherlands). The development of the iPad-app *ReMind* was funded by Health Insurers Innovation Foundation, CbusineZ and 't Hoofdgerecht without commercial interest.

### Investigators and Research Sites

An overview of the participating institutions and researchers involved is provided in Table 1.

**Table 1.** Investigators and research sites of the study

Project member	Role	Research site
GJM Rutten, MD, PhD	Principal investigator, neurosurgeon	Elisabeth-TweeSteden Hospital
SD van der Linden, MSc	PhD student, coordinating investigator	5022 GC Tilburg, The Netherlands
K Gehring, PhD	Project leader, coordinating investigator	Tilburg University
MM Sitskoorn, PhD	Project leader	5000 LE, Tilburg, the Netherlands
CMF Dirven, MD, PhD	Associate investigator	Erasmus Medical Center
DD Satoer, PhD	Associate investigator, contact person EMC	3015 CE Rotterdam, The Netherlands
MJB Taphoorn, MD, PhD	Associate investigator	Haaglanden Medical Center
L Dirven, PhD	Associate investigator, contact person HMC	2501 CK The Hague, The Netherlands

## RATIONALE AND BACKGROUND INFORMATION

Patients with primary brain tumors experience various symptoms, including cognitive deficits. Many factors can cause or aggravate cognitive deficits, for example, the tumor itself, tumor treatment, tumor-related epilepsy or psychological distress.<sup>1,2</sup> Cognitive rehabilitation programs are aimed at alleviating (the impact of) these cognitive deficits.



A few methodologically well-designed studies demonstrated positive effects of cognitive rehabilitation in brain tumor patients.<sup>3,4</sup> However, despite the high need for rehabilitation services and supportive care in brain tumor patients, cognitive rehabilitation programs are not always available or accessible for patients with primary brain tumors in clinical practice.<sup>5-7</sup>

Several years ago, our group conducted a randomized controlled trial (RCT) in 140 patients with glioma on the effects of a face-to-face cognitive rehabilitation program and demonstrated beneficial effects of the program.<sup>3</sup> In a joint patient-researcher initiative, the program was converted into an iPad-based cognitive rehabilitation program, both in Dutch and English, to make the program widely available for patients with primary brain tumors. The content of the program has largely remained the same. We successfully completed a small-scale study to evaluate the feasibility of the use of the renewed program in a clinical (research) setting.<sup>8</sup> Although recruitment of patients appeared to be challenging, patients were satisfied with the program and dropout rate was low. Based on the findings in the feasibility study, adjustments were made to improve the study protocol and the program, before the initiation of a larger RCT. In the RCT, the efficacy of the iPad-based cognitive rehabilitation program will be evaluated. In this manuscript, a detailed description of the study protocol is presented.

## STUDY GOALS AND OBJECTIVES

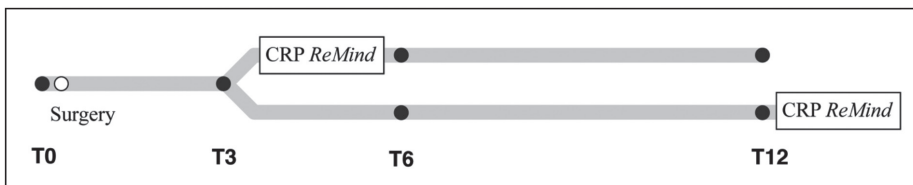
The purpose of this study is to evaluate the immediate and longer-term effects of early cognitive rehabilitation in patients with primary brain tumors. Effects on cognitive performance as determined by neuropsychological testing, as well as effects on patient-reported outcome measures (PROMs) will be evaluated, both on a group level and on an individual level. We hypothesize that early cognitive rehabilitation has beneficial effects on cognitive test performance and PROMs in brain tumor patients recovering from neurosurgery.

The specific objectives are:

1. To investigate the immediate and longer-term effects of early cognitive rehabilitation via the *ReMind*-app on group and individual cognitive performance (i.e., tests of attention, memory and executive functioning).
2. To investigate the immediate and longer-term effects of early cognitive rehabilitation via the *ReMind*-app on group and individual self-reported cognitive functioning, fatigue, psychological distress, community integration and professional functioning.

## STUDY DESIGN

Figure 1 illustrates the design of the study. This prospective, controlled study compares outcomes of two parallel groups, namely an intervention group and a waiting-list control-group, to evaluate the efficacy of an early cognitive rehabilitation program. Adult patients with presumed low-grade glioma and meningioma who will undergo resective surgery are screened for eligibility. Inclusion and exclusion criteria are described in Table 2. Neuropsychological assessments are carried out one day before surgery (T0), three months after surgery (T3; pre-intervention), six months after surgery (T6; post intervention) and twelve months after surgery (T12; half-year follow-up). With the use of this dual baseline design, practice effects can be minimized. In the coordinating center of the study, T0 and T3 assessments are embedded in standard clinical care in the hospital. Immediately after T3, the pre-intervention assessment, patients are allocated in a 1:1 ratio to the intervention group or control group, after which the intervention group follows the cognitive rehabilitation program on a borrowed iPad (Apple Inc., Cupertino, California, United States) for about 10 wk. Immediate effects of the intervention are examined at T6. A half-year later (T12), longer-term effects are evaluated. After completion of all study assessments, patients in the control group have the opportunity to follow the cognitive rehabilitation program.



**Figure 1.** Study Design

Note: CRP = Cognitive rehabilitation program

## METHODOLOGY

### Participants

Between February 2016 and July 2018, patients are included according to the eligibility criteria listed in Table 2. Patients were included in the coordinating center, and two medical centers were recently added. We aim to include 150 participants prior to surgery. With a maximum attrition rate of 33%, 100 patients will be evaluated (50 per group). Every effort will be made to obtain assessments for patients who drop out of the study, to facilitate carrying out intention-to-treat analyses. Prior to the first neuropsychological assessment (T0), informed consent is obtained. Patients can choose to involve an informal caregiver in the study/rehabilitation program. If they choose so, the informal caregiver will have to provide informed consent as well.

**Table 2.** Eligibility Criteria of the Study

<b>Inclusion criteria</b>
<ul style="list-style-type: none"> <li>· Adult patients (age <math>\geq 18</math>)</li> <li>· A supratentorial or infratentorial brain tumor that is radiologically suspect for either a meningioma or low-grade glioma</li> <li>· Resective surgery for this brain tumor</li> </ul>
<b>Exclusion criteria</b>
<ul style="list-style-type: none"> <li>· Tumor resection in the last year</li> <li>· Chemotherapy or radiotherapy in the last 2 years</li> <li>· Presence/history of progressive neurological disease, severe psychiatric disorder or substance abuse</li> <li>· Diagnosis of acute neurological or mild psychiatric disorders in the last 2 years (e.g., CVA)</li> <li>· Multiple (<math>&gt;1</math>) tumors</li> <li>· Lack of basic proficiency in Dutch</li> <li>· Karnofsky Performance Score below 70</li> <li>· IQ below 85, or (very) low cognitive skills</li> <li>· Insufficient reading skills, visual impairment or motor impairment limiting the ability to follow the cognitive rehabilitation program</li> </ul>
<b>Exclusion after informed consent</b>
<ul style="list-style-type: none"> <li>· Severe surgery-related complication (e.g., meningitis or CVA)</li> <li>· Referral to formal cognitive rehabilitation</li> </ul>

## Intervention

The iPad-app *ReMind*, based on our face-to-face cognitive rehabilitation program<sup>3,9,10</sup>, is used in this study. The program consists of psychoeducation, compensation training and retraining. In the compensation training, compensatory strategies are provided, together with fill-in exercises to practice with the strategies in daily life. The retraining includes game-like exercises aimed at training different forms of attention (i.e., sustained, selective, alternating and divided attention). For a detailed description of content of the *ReMind*-app, we refer to our feasibility study.<sup>8</sup> In a first face-to-face meeting with the researcher, patients receive an iPad (Apple Inc., Cupertino, California, United States) with the app installed, so that they can work through the program at home. After this meeting, patients are called every two weeks by the researcher to monitor their progress. It is expected that patients spend approximately 3 h per week on the program to complete the program within 10 wk. Adherence to the program is considered acceptable if patients complete  $\geq 80\%$  of both the strategy training and the retraining. An English version of the app is currently being evaluated in a pilot study in San Francisco (NCT02783495).

### **‘Randomization’ by minimization**

Group assignment takes place immediately after the three-month assessment (i.e., the pre-intervention assessment). Patients are consecutively assigned to the cognitive rehabilitation group and the waiting-list control group in a 1:1 ratio by means of the minimization method, which will balance the groups for age, tumor histology, baseline cognitive performance, physical status and participation in other psychosocial interventions. The minimization method has been proven to provide more balanced groups in smaller trials, compared to restricted (stratified) and unrestricted (simple) randomization.<sup>11</sup> Access to an online minimization program is provided by the Dutch Cancer Institute.<sup>12</sup>

### **Measures**

Outcome measures of the study are listed in Table 3. A computerized neuropsychological test battery, CNS Vital Signs (CNS VS)<sup>13</sup>(CNS Vital Signs, LCC, Morrisville, North Carolina, United States), is administered to measure different aspects of cognitive functioning, including attention, memory and executive functioning. This user-friendly tool can be easily embedded in clinical care, due to rapid administration and semi-automatic processing of results. The battery consists of seven tests, which are based on conventional neuropsychological tests (e.g., Stroop and Symbol Digit Coding). Additionally, three paper-and-pencil (sub)tests were added to the assessment protocol, to measure verbal memory recall<sup>14</sup>, working memory<sup>15</sup> and word fluency<sup>16</sup>; cognitive functions that are not sufficiently covered by the tests of CNS VS (CNS Vital Signs, LCC, Morrisville, North Carolina, United States).

Self-reported cognitive functioning, fatigue and psychological distress are evaluated at all time-points using different questionnaires.<sup>17-19</sup> At T0 and T12, questionnaires on community integration and professional functioning are administered as well.<sup>20-22</sup> Additionally, self-report and proxy-report questionnaires on executive functioning are filled out before (T3) and immediately after (T6) the intervention<sup>23</sup>, and a study specific evaluation questionnaire is administered at T6. This distribution of questionnaires was chosen to minimize patient burden per time point (see Table 3).

Table 3. Overview of neuropsychological tests and questionnaires used in the study

Neuropsychological tests		Cognitive domain(s)	T0	T3	T6	T12
1. Verbal Memory Test (CNS VS) <sup>13</sup>		Verbal memory	X	X	X	X
2. Visual Memory Test (CNS VS) <sup>13</sup>		Visual memory	X	X	X	X
3. Finger Tapping Test (CNS VS) <sup>13</sup>		Psychomotor speed	X	X	X	X
4. Symbol Digit Coding (CNS VS) <sup>13</sup>		Processing speed	X	X	X	X
5. Stroop Test (CNS VS) <sup>13</sup>		Selective attention, cognitive flexibility	X	X	X	X
6. Shifting Attention Test (CNS VS) <sup>13</sup>		Cognitive flexibility	X	X	X	X
7. Continuous Performance Test (CNS VS) <sup>13</sup>		Sustained attention	X	X	X	X
8. Paired Associates (Wechsler Memory Scale-III) <sup>14</sup>		Verbal memory	X	X	X	X
9. Digit Span (Wechsler Adult Intelligence Scale-III) <sup>15</sup>		Working memory	X	X	X	X
10. Letter Fluency <sup>16</sup>		Semantic memory, executive functioning, verbal fluency	X	X	X	X
Questionnaires		PROMs	T0	T3	T6	T12
a. Cognitive Failure Questionnaire (CFQ) <sup>17</sup>		Cognitive complaints	X	X	X	X
b. Multidimensional Fatigue Inventory (MFI) <sup>18</sup>		Fatigue	X	X	X	X
c. Hospital Anxiety and Depression Scale (HADS) <sup>19</sup>		Anxiety and depression	X	X	X	X
d. Community Integration Questionnaire (CIQ) <sup>20</sup>		Independence and participation	X			X
e. Work Ability Index (WAI) <sup>21</sup>		Work ability	X			X
f. Work Limitation Questionnaire (WLQ) <sup>22</sup>		Work limitations	X			X
g. Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) <sup>23</sup>		Executive functioning		X	X	
h. Study-specific evaluation questionnaire (intervention group only) <sup>*</sup>		Experience with the ReMind-program				X

<sup>\*</sup> Patient-report and proxy-report versions are used.

## DISCUSSION

Many patients with primary brain tumors suffer from cognitive deficits, but evidence-based interventions targeting these problems are scarce.<sup>2,24,25</sup> A few studies have been conducted on the effectiveness of cognitive rehabilitation in brain tumor patients, but studies are often hampered by methodological limitations. For example, the majority of previous studies included (very) small sample sizes and/or did not include a control group.<sup>26-30</sup> A decade ago, our RCT demonstrated positive results of our face-to-face cognitive rehabilitation program in 140 glioma patients with stable disease.<sup>3</sup> Shortly thereafter, the RCT of Zucchella and colleagues in 53 brain tumor patients indicated that early cognitive rehabilitation had beneficial effects on cognitive function.<sup>4</sup> Unfortunately, in the last couple of years, very little additional research has been carried out on this topic. More research with larger patient samples and comparison of an intervention group to a control condition is needed, to rule out effects of practice and natural recovery. Also, attention should be paid to the dissemination of the program and the implementation in clinical care.

Therefore, we initiated an RCT on the effects of the iPad-based cognitive rehabilitation program *ReMind*, which was based on our effective face-to-face program and specifically developed for brain tumor patients in a joint patient-researcher initiative. One of the strengths of the study is that both objective cognitive performance as well as patient-reported outcome measures are included. Using relevant questionnaires, insight is gained into patients' daily functioning, which we aim to improve with cognitive rehabilitation. Also, a unique aspect of the study is that informal caregivers are involved. This is important, since brain tumor diagnosis does not only affect the patient, but also the people in his or her environment. Informal caregivers are invited to assist the patient during the intervention and complete a few questionnaires. Besides an extra source of information, involvement of informal caregivers may also be associated with better treatment adherence and less caregiver burden. In addition, patient-proxy agreement on patient's executive functioning can be studied using the completed questionnaires from this study.

Based on previous research and patients' needs, some authors have suggested that cognitive rehabilitation should preferably start as early as possible.<sup>4,7,27</sup> Potentially, this has the advantage that cognitive dysfunction, for example due to adjuvant treatment, can be minimized or prevented. By including a half-year follow-up assessment (T12) in our study, such potential preventive effects can be evaluated.

A weakness of the study may be that patients are not selected based on presence of cognitive deficits/complaints at T0. However, as we expect preventative effects of early cognitive rehabilitation, potential stable good performance in the intervention group versus a decline in the control group may be observed over time. Also, based on our feasibility study<sup>8</sup> and patient recruitment up to now, we expect that accrual of sufficient participants in the RCT will be challenging. This is not only a problem in our study, but a common

phenomenon in studies in cancer patients.<sup>31,32</sup> To increase patient accrual, two additional participating centers are recruiting patients now.

Our study will include a mix of patients with glioma and meningioma. Different types and grades of brain tumors may affect reorganizational processes in the brain in different ways. In addition, varying treatment regimens (radiotherapy and/or chemotherapy or none) that our patients undergo may further impact cognitive functioning. Subgroup analyses in patients with glioma and meningioma separately may help to determine potentially distinctive gains, and maintenance thereof, after cognitive rehabilitation.

To conclude, the effects of an iPad-based cognitive rehabilitation program on cognitive performance and PROMs will be examined in patients with primary brain tumors early in the course of the disease. If this program proves to be effective, we may be able to improve supportive care for brain tumor patients, by implementing this easily accessible cognitive rehabilitation program in clinical practice early after surgery.

## **TRIAL STATUS**

The trial status at the time of submission of this manuscript is recruiting.

## **SAFETY CONSIDERATIONS**

For patients in this study, there are no risks of participation, which is also confirmed by the local medical ethical review board. All Serious Adverse Events (SAEs) are immediately recorded in the Investigator Site File and reported to the local medical ethical review board on a yearly basis.

## **FOLLOW-UP**

Neuropsychological assessments are conducted prior to surgery and 3, 6 and 12 months after surgery. SAEs are reported until the end of the study.

## **DATA MANAGEMENT AND STATISTICAL ANALYSIS**

Data is handled confidentially. A patient identification code list, which is only accessible by direct members of the research team, is used to link the data obtained from neuropsychological testing, questionnaires and medical charts to the participant. Collected data (i.e., pseudonymized paper/digital files) are stored at the coordinating medical center and are only accessible by direct members of the research team. The *ReMind*-app saves data locally on the PIN code protected iPad (Apple Inc., Cupertino, California, United States).

All statistical analyses will be conducted using SPSS version 24, with an alpha set at .05. First, descriptive statistics will be calculated. Subsequently, it will be checked whether the randomization via the minimization method has been successful in balancing the intervention and control group. Then, group analyses on the efficacy of the program will

be conducted on an intention-to-treat basis. Analysis of (co)variance will be conducted to compare mean post intervention scores of the intervention group with mean scores of the control group. Alternatively, we may use linear mixed models that implicitly deal with missing data under the assumption of missing at random.

Since group results may mask the variability in individual responses to the intervention, we also plan to study change at the individual patient level. Reliable Change Indices (RCIs) will be calculated, reflecting change at the individual level in the context of observed changes for the control group of this study.<sup>33</sup> Using this method, possible practice effects, natural recovery and measurement errors are taken into account. Numbers of patients who have improved versus the number of patients who remained stable, or declined, will be compared between groups.

## **QUALITY ASSURENCE**

Annual monitoring is performed by an independent clinical monitor within the hospital. Interim progress reports are sent to the local medical ethical review board and to the funding agency. The principal investigator and coordinating investigator have successfully completed the course on Good Clinical Practice and the study is carried out in accordance with these guidelines.

## **EXPECTED OUTCOMES OF THE STUDY**

After the feasibility study<sup>8</sup>, this randomized controlled trial is the next necessary step towards broader dissemination of the cognitive rehabilitation program. There is a high need for management of cognitive problems and patients do not always find their way to cognitive rehabilitation.<sup>34</sup> As previously described, cognitive rehabilitation programs for brain tumor patients are scarce and research on cognitive rehabilitation in brain tumor patients is lagging. If we are able to demonstrate that cognitive rehabilitation via this eHealth intervention is effective in our sample of meningioma and low-grade glioma patients, the next step will be to make the app widely-available for patients in both Dutch and English.

## **DURATION OF THE PROJECT**

Patient recruitment runs from February 2016 to June 2018. The study ends after the last follow-up assessment one year later, in June 2019.

## **PROJECT MANAGEMENT**

The study is designed and led by the principal investigator dr. Rutten, and project leaders dr. Gehring and prof. dr. Sitskoorn. The treating neurosurgeon/physician assistant identifies eligible patients and provide information about the study. Neuropsychological assessments are carried out by well-trained research assistants. Prior to the first neuropsychological



assessment, informed consent is obtained by the research assistants or the study investigator. The study investigator, Ms. Van der Linden, coordinates the logistics, supervises all patients and manages the data. The investigators will present the findings in manuscripts and on the registered platforms. App maintenance is managed by dr. Gehring.

### **ETHICS**

The study is approved by the local medical ethical review board (METC Brabant/CCMO: P1449, NL51152.028.14) and the study protocol is approved by the institutional review board of each participating center. All substantial changes to the protocol will be re-submitted to the relevant review boards. The study will be conducted in accordance with the Declaration of Helsinki<sup>35</sup> and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). Prior to the first neuropsychological assessment (T0), written informed consent will be obtained from all participants. For ethical reasons, patients in the waiting list control group may borrow an iPad (Apple Inc., Cupertino, California, United States) and follow the cognitive rehabilitation program after completion of all study assessments (Figure 1).

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## CHAPTER 7

# Results of a randomized controlled trial evaluating an iPad-based cognitive rehabilitation program for brain tumor patients



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## ABSTRACT

**Background:** Evidence-based cognitive rehabilitation programs for brain tumor patients are not always available for patients, despite the high needs.

**Objective:** We aimed to evaluate immediate and longer-term effects of an iPad-based cognitive rehabilitation program on cognitive performance and patient-reported outcomes (PROs) in brain tumor patients following neurosurgery.

**Methods:** Patients with presumed low-grade glioma and meningioma were recruited before surgery. Three months after surgery, patients were randomized to the intervention group or waiting-list control group. The 10-week eHealth intervention, based on our effective face-to-face intervention, consisted of psychoeducation, strategy training and attention-retraining. Neuropsychological tests and questionnaires (on cognitive functioning, fatigue and psychological distress) were administered before surgery and 3, 6 and 12 months thereafter. Mean scores over time, percentages of cognitively impaired patients (Z scores  $\leq 1.5$  on <sup>3</sup>1 test) and reliable change indices (RCIs) were compared between groups.

**Results:** Sixty-two out of 330 screened patients were randomized. After randomization, 13 patients dropped out. Patients completed 86% of the strategy training and 91% of the retraining. No significant differences were observed between the intervention group ( $n=23$ ) and controls ( $n=26$ ) over time on group means and RCIs of cognitive performance and PROs. Percentages of cognitively impaired patients were comparable between groups at 3- and 6-months post-surgery ( $\pm 70\%$  of the patients), but 12 months after surgery, there was a significant difference between the intervention group (35%) and control group (68%).

**Conclusion:** Recruitment difficulties were present, resulting in limited power for the analyses. No statistically significant effects of the eHealth intervention on mean scores and RCIs of cognitive performance and PROs were found. For future research on cognitive rehabilitation, intervening at a later stage can be considered.

## INTRODUCTION

Cognitive deficits are common in patients with primary brain tumors.<sup>1-3</sup> Despite the fact that these cognitive deficits are often mild and diffuse in nature, they can lead to problems in social and professional functioning.<sup>4,5</sup> In addition, brain tumor patients often face severe fatigue, psychological distress or language problems<sup>6,7</sup>, which may all contribute to lower quality of life. Particularly, patients with meningioma and glioma patients with favorable prognosis<sup>8,9</sup> live longer with a variety of symptoms, including cognitive deficits. Therefore, treatment of cognitive deficits has become increasingly important in the management of the disease.<sup>10</sup>

The few studies that have been conducted on cognitive rehabilitation in brain tumor patients demonstrated positive effects of cognitive rehabilitation on cognitive outcomes in patients in different stages of the disease, e.g.,<sup>11-15</sup> In a previous randomized controlled trial (RCT) of our group<sup>12</sup>, glioma patients who followed cognitive rehabilitation, consisting of psychoeducation, strategy training and attention retraining, performed better on tests of memory and attention, and reported less cognitive complaints and mental fatigue afterwards. To increase the accessibility of this cognitive rehabilitation program<sup>16</sup> in a cost-efficient and patient-friendly way, we developed an iPad-based version of the program. An initial pilot study demonstrated that post-surgical cognitive rehabilitation via this iPad-app was feasible in patients with meningioma and low-grade glioma.<sup>17</sup>

In this small RCT we investigated the efficacy of the iPad-based program, with respect to cognitive performance and self-reported cognitive functioning, fatigue and psychological distress, in patients with meningioma and low-grade glioma.<sup>18</sup>

## METHODS

The study was conducted in accordance with the Declaration of Helsinki<sup>19</sup> and was approved by the local medical ethical review board (METC Brabant: NL51152.028.14). All participants included in this study provided written informed consent. Greater details regarding the methods, materials and intervention used in this study were described in a previously published study protocol.<sup>18</sup>

### Participants

Prior to surgery, adult patients with presumed low-grade glioma or meningioma were included at the Elisabeth-TweeSteden Hospital Tilburg, Haaglanden Medical Center the Hague and Erasmus Medical Center Rotterdam. Based on power analyses, it was projected to include 150 patients before surgery. With a maximum attrition rate of 33%, we aimed to evaluate data from 100 patients (50 per group). Patients were not eligible if: they had multiple brain tumors; had undergone brain tumor resection in the last year;



had had chemotherapy or radiotherapy in the last two years; had a history of progressive neurological disease/severe psychiatric disorders or substance abuse; had been diagnosed with acute neurological/psychiatric disorders in the last two years; lacked a basic proficiency in Dutch; had an IQ below 85; had a KPS below 70; or had visual, language or motor impairments limiting participation in the study (the ability to complete neuropsychological assessment and/or to follow the iPad-based program). After surgery patients were also excluded if they suffered from surgery-related complications or if they were referred to cognitive rehabilitation elsewhere.

### Design and procedure

Patients in this multicenter prospective RCT were invited to participate prior to surgery. After patients' approval, informal caregivers were also invited to participate. Patients underwent neuropsychological assessments before surgery (T0) and three months after surgery (T3). At T3, patients were assigned to the intervention group or to the waiting-list control group. The minimization method<sup>20</sup> was used to balance groups for age, tumor histology, baseline cognitive test performance, physical health status (ASA score) and participation in other psychosocial interventions. Software was provided by the Netherlands Cancer Institute Amsterdam.<sup>21</sup> Neuropsychological follow-up assessments were conducted immediately after the intervention (six months after surgery; T6) and one year after surgery (T12). Caregivers were asked to complete a questionnaire on the patient's executive functioning and a study-specific evaluation questionnaire. Patients in the waiting-list control group were offered the opportunity to follow the cognitive rehabilitation program after the last assessment.

### Intervention

The iPad-based cognitive rehabilitation program *ReMind* includes psychoeducation, strategy training and an attention retraining game. The psychoeducational information and strategy training are spread over six modules, namely (1) Cognitive functions, (2) Influences, (3) Compensation, (4) Attention, (5) Planning & Control, and (6) Memory. The program includes several technical features to provide support, for example the possibility of using videos/audio clips in addition to written information, and help-overlay screens. The retraining exercises are aimed at sustained, selective, alternating and divided attention. After the feasibility study<sup>17</sup>, we made a few adjustments to the iPad-based rehabilitation program, based on the feedback of the pilot participants, for example the addition of more (complex) retraining exercises. For more details on the content of *ReMind*, we refer to the publication on our feasibility study.<sup>17</sup>

The advice to patients was to spend 3 hours a week on the program, to complete the program in 10 weeks. During the intervention, assistance was provided by the researcher through telephone assistance every two weeks, and if desired by their informal caregiver.

### Outcome measures

*Enrollment and attrition.* The number of patients invited to participate was recorded, as were the numbers of patients who agreed or declined. Reasons for decline, and later, reasons for dropout, were recorded as well.

*Adherence and patient satisfaction.* The number of completed modules in the strategy training and the number of completed exercises in the retraining, each expressed in percentages, were used to measure adherence to the program. Adherence was considered sufficient if patients completed  $\geq 80\%$  of both the strategy training and the retraining. A maximum of 100% per individual was used to calculate mean adherence rates, even if patients worked through the program more than once. Experiences of patients, and of informal caregivers if involved, with the iPad-based program were evaluated post-intervention, with a study-specific evaluation questionnaire.<sup>17</sup>

*Performance-based cognitive outcomes.* Cognitive functioning was measured with the computerized neuropsychological test battery Central Nervous System Vital Signs (CNS VS, LCC, Morrisville, North Carolina).<sup>22</sup> CNS VS consists of seven tests, assessing the following domains: verbal memory, visual memory, processing speed, psychomotor speed, reaction time, complex attention and cognitive flexibility. Additionally, working memory was assessed with the Digit Span Test of the Wechsler Adult Intelligence Scale (WAIS-III), and verbal fluency was measured with a Letter Fluency test.<sup>23</sup> Patient scores were converted to Z scores (correcting for age, sex and/or education) using Dutch norms.<sup>23-25</sup> Z scores  $\leq -1.5$  indicated impaired cognitive functioning.

*Patient reported outcomes (PROs).* The Cognitive Failures Questionnaire (CFQ) was used to measure self-reported cognitive failures. Additionally, two index scores of the Behaviour Rating Inventory of Executive Function (BRIEF-A) were evaluated, namely Behavioral regulation and Metacognition. Two subscales of the Multidimensional Fatigue Inventory (MFI-20) were also included, to measure the level of physical fatigue and mental fatigue. Symptoms of anxiety and depression were examined using the Hospital Anxiety and Depression Scale (HADS). Scores were converted to Z scores based on published norms<sup>26-29</sup> and again, Z scores  $\leq -1.5$  were considered as low.

### Statistical analysis

Statistical analyses were conducted using SPSS version 24 (IBM Inc, Armonk, New York), with alpha set at .05. Preintervention (T3) sociodemographic and clinical characteristics were compared between the intervention and control group using independent sample

t-tests, Chi-square tests and Fisher's exact tests, depending on the distribution of the tested variable. Preintervention neuropsychological scores were also compared between groups.

To evaluate potential differences in outcome with respect to cognitive performance tests and PROs over time between the intervention group and control group, repeated measures ANOVAs were used. Standardized scores of cognitive performance-based outcomes and PROs on T3, T6 and T12 were each included as dependent variables in the series of analyses, with 'group' (intervention versus controls) as between-subject factor. Additionally, mean within-group changes were presented in bar charts. Chi-square tests were conducted to evaluate frequencies of patients with impairment ( $Z$  scores  $\leq -1.5$ ) at each time-point.

Reliable change indices (RCIs) were calculated for the performance-based outcomes and PROs. RCIs reflect change in individual patient scores relative to observed changes in the control group, thus taking into account practice effects, natural recovery and measurement errors.<sup>30</sup> Reliable improvement was defined as RCI values above +1.645 and decline below -1.645 (based on an alpha of .10, corresponding to a 90% confidence interval). RCIs were calculated over the first time-interval (T3-T6) and over the second interval (T3-T12). Numbers of patients who reliably improved/declined on one or more outcomes were compared between groups for the performance-based outcomes and PROs separately using Chi-square tests.

## RESULTS

### Enrollment and attrition

Figure 1 presents the flow of patients throughout the trial. Prior to surgery, 330 patients with presumed meningioma and low-grade glioma were screened for eligibility. Based on the inclusion/exclusion criteria, 183 patients were eligible and were invited to participate at T0, of whom 84 declined participation and 99 provided written informed consent. Most important reasons for decline were that (patients anticipated that) it would be too burdensome and/or too time-consuming ( $n=47$ ); they had no affinity with iPads/computers ( $n=13$ ); or that they felt no need because of the absence of cognitive complaints ( $n=7$ ). From surgery to T3, i.e. before randomization, 37 patients dropped out of the study. Most important reasons were lack of motivation ( $n = 14$ ; including 8 patients who wanted to devote full attention to work resumption) and referral to conventional cognitive rehabilitation ( $n=11$ ).

Three months after surgery, 62 patients were randomized to the intervention or control group. Between T3 and T6, 8 patients in the intervention group dropped out the study and 5 controls. Between T6 and T12, 3 intervention group patients and 1 control dropped out

(Figure 1). As a result, T6 data of 23 patients in the intervention group and 26 in the control group and T12 data from 20 and 25 patients were analyzed.

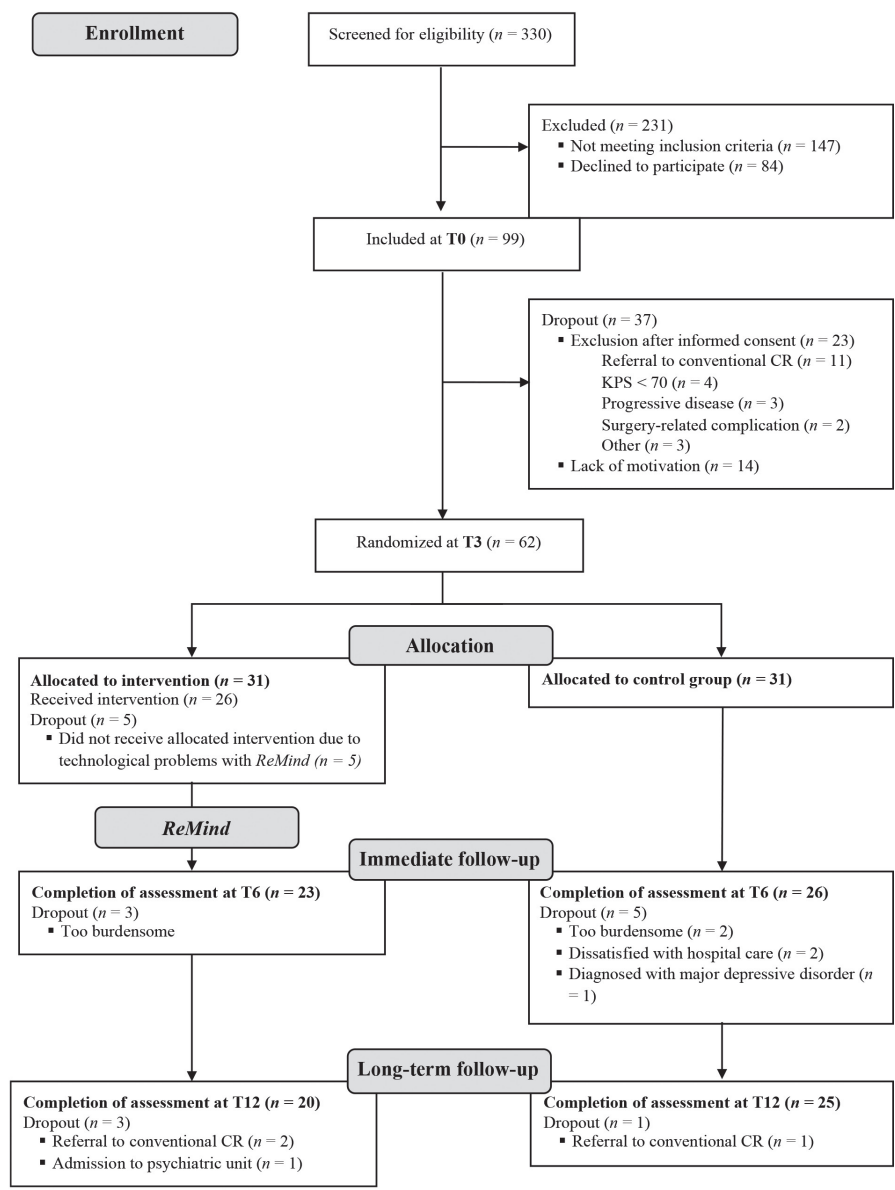
### Patient characteristics

Sociodemographic and clinical characteristics of the intervention and control group are listed in Table 1. Patients in the intervention group were significantly younger than the controls ( $M_{diff} = -6.92, p = .03$ ). Also, in the intervention group, the percentage of women was significantly higher compared to the control group (74% vs 46%,  $p < .05$ ). Sixteen patients in the intervention group (70%) and 20 patients in the control group (77%) chose to involve an informal caregiver (Table 1). Mean pre-intervention scores on the performance-based outcomes and PROs did not differ significantly between the intervention group and control group (all  $p$ -values  $> .05$ ).

### Adherence and patient satisfaction in the intervention group

The twenty-three patients completed on average 86% of the strategy training and 91% of the retraining. Sufficient adherence (completion of  $\geq 80\%$  of both the strategy training and retraining) was observed in 16 patients (70%). Furthermore, 14 patients completed the retraining more than once.

The evaluation questionnaire was fully completed by 21 patients, and partly by one other patient (Table 2). Overall, 90% of patients rated to program as “good” or “excellent”, and 95% would recommend the program to other brain tumor patients. The difficulty and amount of information in the strategy training was perceived as sufficient and patients indicated that the information was useful. However, a substantial part of the patients ( $n=14$ ) indicated that there were too many fill-in exercises included in the strategy training. Furthermore, 11 patients reported that there were (too) few exercises included in the retraining and 13 that the retraining was (too) easy, but nevertheless the retraining exercises were perceived as (very) useful by 19 patients. Twenty patients indicated to have appreciated the iPad-based delivery of the program and 16 patients indicated that the two-weekly telephone assistance was (very) useful.



**Figure 1.** Flow of participants through the trial

Note: CR = Cognitive Rehabilitation; KPS = Karnofsky Performance Status

**Table 1.** Sociodemographic and clinical characteristics of intervention group and control group

Characteristic	Intervention group (n = 23)	Control group (n = 26)	p-value
Age at T3 (Mean; SD)	45.7 (11.7)	52.6 (10.4)	.033*
Sex (n female; %)	17 (74%)	12 (46%)	.048*
Years of education (Mean; SD)	15.4 (3.6)	15.1 (3.6)	.766
Level of education (n; %)			.334
Low	4 (17%)	5 (19%)	
Middle	4 (17%)	9 (35%)	
High	15 (65%)	12 (46%)	
Physical status (n; %) <sup>a</sup>			1.00
ASA I/II	23 (100%)	25 (96%)	
ASA III/IV	-	1 (4%)	
Tumor histology (n; %) <sup>b</sup>			.821
Meningioma (grade I)	13 (57%)	14 (54%)	
Atypical meningioma (grade II)	1 (4%)	1 (4%)	
Grade II glioma	9 (39%)	10 (39%)	
Grade III glioma	-	1 (4%)	
Tumor hemisphere <sup>c</sup> (n; %)			.681
Left	11 (48%)	11 (42%)	
Right	11 (48%)	14 (54%)	
Bilateral	1 (4%)	1 (4%)	
Radiotherapy after surgery <sup>a,d</sup> (n; %)	4 (17%)	10 (39%)	.103
Chemotherapy after surgery <sup>d</sup> (n; %)	3 (13%)	7 (27%)	.299
Psychotropic medication at T3 (n; %)	11 (48%)	17 (65%)	.215
Cognitive impairment <sup>e</sup> at T3 (n; %)	16 (70%)	16 (69%)	.980
Low PRO scores <sup>f</sup> at T3 (n; %)	14 (61%)	18 (69%)	.539
Involvement of informal caregiver	16 (70%)	20 (77%)	.339

<sup>a</sup> Fisher's Exact Test was interpreted, since not all cell counts were greater than five.

<sup>b</sup> Proportions of patients with meningioma and glioma were compared between groups (not separated by tumor grade).

<sup>c</sup> Patients with bilateral tumors were excluded for the statistical comparison.

<sup>d</sup> During study participation (i.e. within one-year post-surgery)

<sup>e</sup> Z score  $\leq -1.5$  on one or more performance-based outcomes

<sup>f</sup> Z score  $\leq -1.5$  on one or more PROs

**Table 2.** Post-intervention ratings of different aspects of *ReMind* (n = 22)

<b>Difficulty of</b>	<b>(too) easy</b>	<b>just right</b>	<b>(too) difficult</b>
Information in strategy training	7	13	2
Fill-in exercises in strategy training	9	7	4
Retraining (C-Car game)	13	8	-
<b>Amount/number of</b>	<b>(too) little/few</b>	<b>about right</b>	<b>(too) much/many</b>
Information in strategy training	1	19	2
Fill-in exercises in strategy training	-	7	14
Retraining exercises (C-Car game)	11	10	1
Supervision of the researcher/trainer	-	22	-
<b>Usefulness of</b>	<b>(very) useful</b>	<b>neutral</b>	<b>not useful</b>
Information in strategy training <sup>a</sup>	14	5	2
Fill-in exercises in strategy training <sup>a</sup>	5	10	5
Retraining exercises (C-Car game)	19	2	1
(telephone) contact with the researcher/ trainer	16	6	-
Content addressed daily problems	<b>fully/largely</b>	<b>partly</b>	<b>not</b>
	10	7	4
Application of learnt (strategies) in daily life	<b>often/regularly</b>	<b>sometimes</b>	<b>seldom/never</b>
	9	7	6
Impact of cognitive problems has changed	<b>yes, positively</b>	<b>no<sup>b</sup></b>	<b>yes, negatively</b>
	10	11	-
Coping with cognitive problems has changed	<b>improved coping</b>	<b>no<sup>c</sup></b>	<b>worsened coping</b>
	6	16	-
Pleasantness of working on <i>ReMind</i>	<b>(very) pleasant</b>	<b>neutral</b>	<b>(very) unpleasant</b>
	7	14	-
	<b>excellent/good</b>	<b>sufficient</b>	<b>insufficient/poor</b>
Using an iPad-app for cognitive rehabilitation	20	2	-
Capability of the researcher/trainer	20	2	-
Contact with the researcher/trainer	21	1	-
Overall rating of the program	19	1	1

Table 2. Continued

	yes	no
Recommendation to other brain tumor patients	21	1

<sup>a</sup>Missing values for two participants

<sup>b</sup>No change, there was no impact on daily life (7) or no change, impact remained the same (4)

<sup>c</sup>Coping is still good (14), or coping is still not good (2)

### Evaluation of mean scores on cognitive performance and PROs

Mean scores of the groups at the different time points are listed in Table 3 and mean changes over time in both groups are presented in Figure 2. Repeated measures ANOVAs demonstrated no significant interaction effects of time and group on the outcome variables (all  $p$ -values  $>0.05$ ). Regarding cognitive performance, significant positive main effects of time (irrespective of group) were observed for processing speed, complex attention, cognitive flexibility and working memory. For the PROs, positive main effects of time were found, indicating fewer concerns with respect to behavioral regulation, metacognition and mental fatigue.

### Evaluation of impairment on cognitive performance and PROs

Proportions of patients in the intervention group and control group, who scored below the cutoff ( $Z$  scores  $\leq -1.5$ ) on one or more performance-based outcomes pre- and immediately post-intervention (T3 and T6), were not significantly different between the groups, with percentages lying around 70% (Table 3). At T12, significantly fewer patients in the intervention group showed cognitive impairment, with 35% of the patients in the intervention group scoring low on one or more performance-based outcomes vs 68% of the control group ( $p=.027$ ). Regarding PROs, no significant between-group differences were observed for any of the time-points.

### Individual-level change in cognitive performance and PROs

Over the first interval (T3-T6), 48% of the patients in the intervention group and 23% of the patients in the control group showed reliable improvements on one or more performance-based outcomes, and reliable decline was observed in 30% vs 15% of the patients (Table 4). Between T3 and T12, improvement was observed in 35% of the patients in the intervention group vs 24% of the controls, and decline in respectively 20% vs 32% (all  $p$ 's  $>.05$ ).

Over the first interval, 83% patients in the intervention group, and 89% of the controls improved reliably on one or more PROs. Reliable decline was observed in 30% and 19% of the patients in the intervention group and control group respectively. Over the long-term, improvements were observed for 85% of the patients in the intervention group vs 72% of

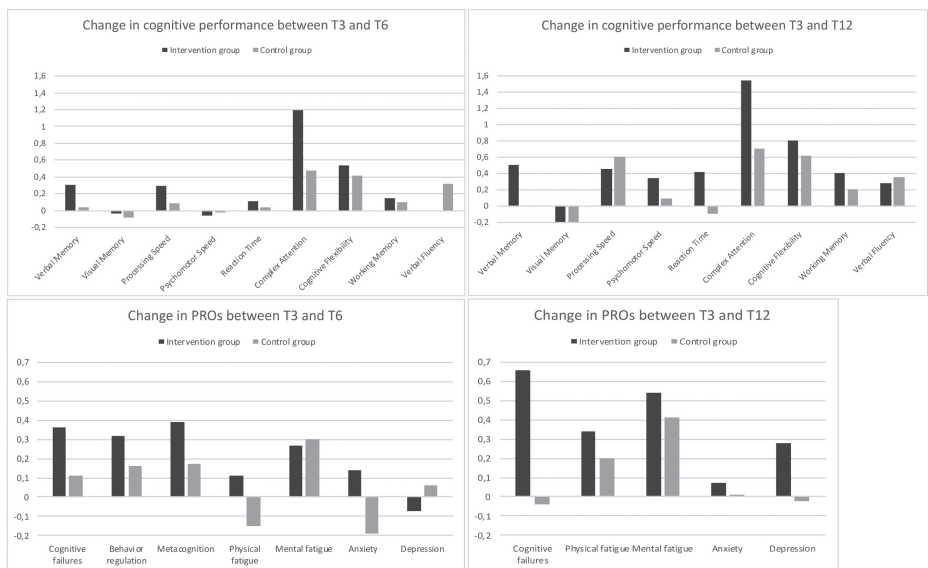


the controls, and decline was observed in 10 vs 20% respectively (Table 4). None of the differences in proportions were statistically significant ( $p>.05$ ).

**Table 3.** Mean scores of the intervention group and control group on cognitive performance and PROs per time-point

	Intervention group			Control group		
	T3 (n = 23)	T6 (n = 23)	T12 (n = 20)	T3 (n = 26)	T6 (n = 26)	T12 (n = 25)
<b>Cognitive performance outcomes</b>						
Verbal memory	-0.41	-0.10	0.09	-0.68	-0.64	-0.68
Visual memory	0.13	0.09	-0.07	-0.37	-0.45	-0.56
Processing Speed	-0.36	-0.07	0.09	-0.60	-0.51	0.00
Psychomotor Speed	-0.22	-0.28	0.12	-0.36	-0.38	-0.27
Reaction Time	-0.55	-0.44	-0.13	-1.36	-1.32	-1.46
Complex Attention	-1.54	-0.35	0.00	-1.22	-0.75	-0.51
Cognitive Flexibility	-0.98	-0.45	-0.18	-1.19	-0.77	-0.57
Working Memory	-0.06	0.09	0.34	-0.05	0.05	0.15
Verbal Fluency	-0.34	-0.33	-0.05	-0.60	-0.28	-0.25
Impaired on $\geq 1$ performance-based outcomes (n; %)	16/23 (70%)	15/23 (65%)	7/20 (35%)	19/26 (73%)	18/26 (69%)	17/25 (68%)
<b>Patient Reported Outcomes</b>						
Cognitive complaints (CFQ)	-0.43	-0.07	0.23	0.12	0.23	0.08
Behavioral Regulation (BRIEF-A)	-0.13	0.19	-	0.10	0.26	-
Metacognition (BRIEF-A)	-0.66	-0.27	-	-0.41	-0.24	-
Physical fatigue (MFI)	-0.63	-0.52	-0.29	-0.66	-0.81	-0.46
Mental fatigue (MFI)	-0.96	-0.69	-0.42	-1.04	-0.74	-0.63
Anxiety symptoms (HADS)	0.12	0.26	0.19	0.18	0.37	0.38
Depressive symptoms (HADS)	-0.02	-0.09	0.26	0.19	0.13	0.11
Impaired on $\geq 1$ PRO (n; %)	14/23 (61%)	9/23 (39%)	5/20 (25%)	18/26 (69%)	14/26 (54%)	13/25 (52%)

Note: Higher mean scores indicate better outcomes



**Figure 2.** Mean changes in Z scores over the first (T3-T6) and second (T3-T12) interval for the intervention group and control group

Note: Positive change scores indicate improvement on the outcome variables, whereas negative scores indicate decline.

Table 4. Reliable individual-level change in the intervention and control group

	Intervention group				Control group			
	Change between T3-T6		Change between T3-T12		Change between T3-T6		Change between T3-T12	
	Improvement	Decline	Improvement	Decline	Improvement	Decline	Improvement	Decline
Cognitive performance outcomes								
No reliable change (n; %)	12/23 (52%)	16/23 (70%)	13/20 (65%)	16/20 (80%)	20/26 (77%)	22/26 (85%)	19/25 (76%)	17/25 (68%)
Reliable change on <sup>3</sup> 1 outcome (n; %)	11/23 (48%)	7/23 (30%)	7/20 (35%)	4/20 (20%)	6/26(23%)	4/26 (16%)	6/25(24%)	8/25 (32%)
Patient Reported Outcomes								
No reliable change (n; %)	4/23 (17%)	16/23 (70%)	3/20 (15%)	18/20 (90%)	3/26 (12%)	21/26 (81%)	7/25 (28%)	20/25 (80%)
Reliable change on <sup>3</sup> 1 outcome (n; %)	19/23 (83%)	7/23 (30%)	17/20 (85%)	2/20 (10%)	23/26 (88%)	5/26 (19%)	18/25 (72%)	5/25 (20%)

## DISCUSSION

In this RCT, the effects of the iPad-based cognitive rehabilitation program starting three months after surgery were evaluated in 49 patients with low-grade glioma and meningioma. Recruitment of patients before surgery was challenging, only 19% of the patients who were screened were randomized at T3. A substantial proportion of included patients (37%) dropped out in the first three months after surgery and before randomization. Adherence rates of the patients who followed the intervention were sufficient, with patients completing on average 86% of the strategy training and 91% of the retraining. Moreover, patients evaluated the program positively.

Although mean changes over time for cognitive performance and PROs were generally larger in the intervention group than in the control group, no significant effects were found at group level. Also, in the evaluation of individual reliable change in cognitive performance and PROs, we found no significant differences in proportions between the intervention group and controls. Percentages of patients with cognitive impairment were comparable between groups at T3 and T6 ( $\pm 70\%$ ), but at T12, a significant difference in proportions was found between the intervention group (35%) and controls (68%). This, however, may be partly explained by the fact that pre-intervention scores of the patients in the intervention group were already (not statistically, but still a little) higher. Post-surgical cognitive improvements over time in both groups, due to amongst other natural recovery, may have led to a higher percentage of patients in the intervention group scoring within normal (non-impaired) ranges at T12. On the other hand, one may argue that in the control group with observed lower scores there was more room for improvement, which was not seen.

Our previous RCT, evaluating the face-to-face version of the cognitive rehabilitation program in lower-grade glioma patients with cognitive complaints and disorders, demonstrated small to medium positive effects on self-reported mental fatigue and performance on memory and attention tests.<sup>12</sup> In contrast, we found no beneficial effects of the iPad-based cognitive rehabilitation program in the current RCT. Several differences may explain null findings of the current trial, including 1) the small sample size, 2) early timing of the intervention, 3) inclusion of patients independently of cognitive complaints/disorders, and/or 4) limited follow-up period. Still, lessons learned from the current study can guide future research on (eHealth) cognitive rehabilitation in brain tumor patients.

Compared to our current RCT in 49 brain tumor patients, many more patients were enrolled in our previous study ( $n=140$ ), resulting in differences in statistical power for the analyses. Initially, we aimed to include 100 patients (50 per group), but recruitment of patients, and also the retention of patients, was difficult. Unfortunately, recruitment problems are common in psycho-oncological studies, especially in RCTs.<sup>31,32</sup> Many patients were not eligible for randomization according to the in/exclusion criteria (i.e. 170/330; 52%). In addition, a substantial part of patients declined participation. Reasons for decline varied,

but many patients ( $n=47$ ) mentioned that they would expect it to be too burdensome for them. Of course, the targeted patients face a complex period of time after surgery, in which they need time for recovery, adjuvant treatment, coping with their diagnosis and symptoms, and want to devote their time to family, home, work resumption, and social and leisure activities. This seems particularly the case in this group, since patients are relatively young and carry many responsibilities.

Given that a very large proportion of brain tumor patients experience cognitive deficits at a certain point during the disease trajectory, we chose to adopt a preventive and inclusive approach in this study. We included patients based on their willingness to participate at an early stage of the disease, and not based on the presence of cognitive deficits or complaints, which was the case in our previous RCT.<sup>12</sup> Also, both meningioma and low-grade glioma were included in the study, who may respond to cognitive rehabilitation in different ways. Unfortunately, the size of our sample did not allow for subgroup analyses on differences in outcomes for meningioma vs glioma, adherent vs non-adherent patients and patients who involved an informal caregiver vs patients who did not. Furthermore, it is possible that any positive preventative effects of the intervention may occur at a later stage (>6-months post-intervention), which would have required a longer follow-up period.

The effectiveness of our face-to-face program<sup>12</sup> implies that certain ingredients of the program can lead to improvements in cognitive functioning in brain tumor patients. However, in the current study use was made of eHealth instead of the face-to-face cognitive rehabilitation. To our knowledge, this is the first study on eHealth cognitive rehabilitation in brain tumor patients. eHealth is a relatively new and rapidly evolving field of research, and it is also promising, since it has the potential to deliver intervention programs to many patients in a cost-efficient way. Studies have demonstrated that psychological eHealth interventions can be as effective as face-to-face programs.<sup>34,35</sup> However, accumulating evidence also suggests that with an increasing amount of support, moving towards a more blended care approach, psychological eHealth interventions yield better results.<sup>36,37</sup> Although patients appreciated the two-weekly telephone assistance and could receive help from their informal caregiver, it is possible that our intensive cognitive rehabilitation program requires more intensive guidance of a professional, to achieve beneficial effects for brain tumor patients.

Intervention studies make use of strict protocols, in order to be able to demonstrate potential beneficial effects of the intervention. In clinical practice, neuropsychological interventions are often more tailored to the needs and situations of patients and family members. Given the heterogeneity of brain tumors and existing individual variability, it would have been interesting to identify characteristics of patients who may benefit from cognitive rehabilitation, and patients who do not.<sup>33</sup> Although, despite the current findings, we believe that early intervention can still be beneficial for some patients, recruitment

of patients for participation in research was very time-consuming at this early stage. For follow-up research on (eHealth) cognitive rehabilitation, we would suggest a later timing of the intervention (e.g., in patients with stable disease), based on our findings with respect to the recruitment of patients.<sup>12</sup> In this way, larger samples may be recruited allowing for firmer conclusions with respect to effectiveness of the intervention.

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## **CONFLICT OF INTEREST STATEMENT**

The authors declare that there is no conflict of interest.

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## OVERVIEW OF THE FINDINGS

In the studies of the first part of the dissertation, different aspects of neuropsychological assessment of cognitive function and fatigue were investigated in patients with brain tumors, followed by the second part of the thesis which focused on cognitive rehabilitation via the *ReMind*-app.

In **chapter 2**, we evaluated test-retest reliability and potential practice effects of the computerized neuropsychological test battery CNS Vital Signs in a sample of Dutch healthy adults. At baseline, 158 participants were included and at 3- and 12-months follow-up, 131 and 77 participants were reassessed. Test-retest correlations coefficients varied widely across cognitive domains (ICCs ranging between .40 and .88). Regarding practice effects, it was shown that participants scored significantly better on the Stroop Test, Shifting Attention Test and Symbol Digit Coding Test at the 3-month retest, resulting in significantly higher scores on the domains of Cognitive Flexibility, Processing Speed, and Reaction Time. No significant changes in performance were demonstrated between the second and third assessment. RCI-formulae were formulated to correct for imperfect test-retest reliability and practice effects and can be used in clinical care, to facilitate proper interpretation of individual change in cognitive performance on the CNS VS.

In **chapter 3**, a closer look was taken at executive functioning of patients with low-grade glioma and meningioma, using self-report, proxy-report and test performance measures. Agreement on patients' executive functioning (EF) was examined in 47 brain tumor patients and their proxies. Self-report of patients was compared with proxy-report three months post-surgery. Furthermore, associations of reported measures of EF with performance-based measures of EF were evaluated, as well as the influences of these performance-based measures on the level of patient-proxy agreement. Patients reported significantly more problems on the Metacognition index of the BRIEF-A in comparison with norms, and also in comparison with proxies. Overall, patient-proxy agreement was found to be moderate, and no clear associations were found between reported measures of EF and executive test performance. The mismatch between patient reports and cognitive test performance can be further investigated, as well as potential innovative methods to assess everyday EF in brain tumor patients.

In **chapter 4**, prevalence, severity and correlates of fatigue were investigated in patients with grade I meningioma using a validated multidimensional questionnaire. Before surgery ( $n = 65$ ) and one year after surgery ( $n = 53$ ), meningioma patients scored significantly higher on all subscales of the MFI compared to normative values. In a subgroup of patients who underwent both assessments ( $n = 34$ ), mean scores for General Fatigue, Physical Fatigue and

Mental Fatigue remained stable over time and improvements were observed for Reduced Motivation and Reduced Activity. At the individual level, 68% of the patients scored high (Z score  $\geq 1.3$ ) on one or more subscales of the MFI before surgery. Postoperatively, 57% still scored high on one or more subscales. Furthermore, fatigue was associated with self-reported cognitive complaints, anxiety and depression. From this study, it became clear that fatigue is a serious, common and persistent symptom in patients with meningioma who underwent neurosurgery, that needs more attention of clinicians and researchers in the field of neuro-oncology.

Then, moving towards rehabilitation of cognitive functioning, in **chapter 5**, our pilot study on the iPad-based cognitive rehabilitation program *ReMind* was presented. Feasibility of, and potential barriers to, the use of program in the clinical (research) setting were evaluated in 15 patients with meningioma and glioma. The cognitive rehabilitation program, based on the previously evaluated face-to-face program of Gehring and colleagues (Gehring et al., 2009), consists of psychoeducation, compensation training and retraining of attention. Recruitment of participants prior to surgery was challenging, as 57% of the patients who were scheduled for neurosurgery were not eligible, and of the patients who were invited to participate, 46% declined participation. Furthermore, participants completed on average 71% of the compensation training and 76% of the retraining. Overall, participants were satisfied with the program and dropout was low (13%). Participants reported that an iPad-app was an appropriate mode of delivery of the program. Some patients evaluated the retraining part of the program as too easy, and therefore, the it was expanded with more difficult exercises.

Subsequently, a larger randomized trial (RCT) was started to evaluate the efficacy of the iPad-based cognitive rehabilitation program *ReMind* with respect to cognitive outcomes and patient-reported outcomes (PROs). In **chapter 6**, the study protocol of our RCT was described in detail. We aimed to include 150 patients with meningioma and low-grade glioma prior to surgery. With a maximum attrition rate of 33%, 100 patients (50 per group) were expected. Neuropsychological assessments were carried out before surgery (T0) and three months thereafter (T3). At T3, patients were randomly assigned to the intervention group or waiting-list control group, and patients in the intervention group again followed the cognitive rehabilitation program *ReMind* for 10 weeks. Patients were neuropsychologically retested six months (T6) and twelve months (T12) after surgery.

In **chapter 7**, we presented the results of this RCT. Similar to the pilot study, recruitment of patients was difficult, which led to the inclusion of a relatively small sample of patients for the analyses (intervention group  $n = 23$ , controls  $n = 26$  at T6). Adherence to the

program was higher than in the pilot study, with patients completing on average 86% of the compensation training and 91% of the retraining. Dropout rate on the other hand, was higher in the RCT than in the pilot study. Comparing mean scores of patients in the intervention group and control group on performance-based outcomes and PROs using repeated measures ANOVAs did not indicate statistically significant differences. Also, no significant differences between the intervention group and control group were observed in proportions of patients who improved or declined reliably. Percentages of patients with cognitive impairment were comparable at T3 and T6 (percentages around 70%), but one year after surgery 35% of the patients in the intervention group vs 68% of the controls showed impaired scores on one or more cognitive domains, which was a significant difference. For follow-up research on (eHealth) cognitive rehabilitation, we would suggest a later timing of the intervention (e.g., in patients with stable disease), based on our findings with respect to the recruitment of patients.

### **ROUTINE ASSESSMENT OF COGNITIVE FUNCTION: WHY, WHAT AND HOW?**

Brain tumor diagnosis and its treatment have major impact on patients' lives. Many patients suffer from various symptoms including cognitive deficits, fatigue and psychological distress. In turn, these symptoms can lead to impairments in daily functioning and lowered quality of life of patients.<sup>1,2</sup> For clinicians, it is important to pay attention to these symptoms during the disease process, in order to be able to provide appropriate care timely. In addition, lower cognitive performance on preoperative neuropsychological tests can be predictive for worse late cognitive outcomes.<sup>3</sup> Accurate prediction of postoperative cognitive performance can aid both the patient and clinician in medical decision-making and determine best treatment option for the individual patient.

A necessary first step is that cognitive symptoms should be detected and therefore, systematic assessment is crucial. However, cognitive performance on neuropsychological tests is not strongly correlated with self-perceived cognitive functioning as reported on questionnaires (see chapter 3 and <sup>4,5</sup>). Previous research has shown that self-reported cognitive functioning seems more strongly associated with symptoms of anxiety, depression and fatigue<sup>4,6</sup>, which was also demonstrated in our fatigue study in meningioma (chapter 4). Possible explanations for the mismatch between cognitive performance and self-reported cognitive functioning are, for example, that ecological validity of neuropsychological tests is limited and/or that self-report of cognitive functioning is hampered by self-report biases. Still, patients' report on their cognitive functioning does not allow conclusions about their objective cognitive function and vice versa. For routine assessment in brain

tumor patients, we recommend the use of a short and efficient neuropsychological test battery, together with a concise screening questionnaire assessing cognitive functioning, psychosocial functioning and fatigue. For instance, the Distress Thermometer and Problem List<sup>7</sup> can be used as a screening questionnaire, which could also be administered digitally. In addition, the inclusion of long-term follow-up assessment is very important, since cognitive symptoms or fatigue may manifest or aggravate later (for example, due to late effects of radiotherapy). It can also be that some patients become aware of these symptoms at a later stage, because of increasing demands (e.g., return to work and social obligations).<sup>6</sup>

Lastly, informal caregivers should be actively involved in the disease trajectory of patients. They can provide valuable information on functioning of the patient, when the patient is not able to provide the information him/herself. In our study on patients' executive functioning (EF) it was demonstrated that proxy-report is a reasonable estimate of patient-report of EF, which was in line with other studies on patient-proxy agreement on, amongst others, quality of life in brain tumor patients.<sup>8,9</sup> Moreover, it is important to have insight in caregiver burden and caregiver's quality of life, since caregivers are often confronted with multiple challenges, among which are dealing with a variety of symptoms, financial issues, changing roles and difficulties in communication.<sup>10</sup> Appropriate care should be provided in time. Psychoeducation timely in the disease process, as for example incorporated in the *ReMind*-app, may be an important first step for both patients and caregivers. Furthermore, caregivers can benefit from information and concrete advice on coping with everyday difficulties<sup>10</sup> and sometimes, referral to a clinical psychologist for psychological treatment can be necessary.

## COGNITIVE REHABILITATION: HELPFUL OR NOT?

In different patient populations, positive effects of cognitive rehabilitation have been demonstrated.<sup>11-13</sup> Also, in brain tumor patients, promising effects of cognitive rehabilitation have been reported.<sup>14</sup> In the evaluation of our eHealth cognitive rehabilitation program *ReMind*, we found that post-surgical cognitive telerehabilitation was feasible in brain tumor patients and that patients were satisfied with the program in our pilot study (chapter 5). However, no significant effects were found on mean scores and RCIs of cognitive outcomes and PROs between the intervention and control group in our RCT (chapter 7). The finding of our RCT were in contrast with the previous study of our group, which demonstrated beneficial effects of the original face-to-face-cognitive rehabilitation program.<sup>15</sup> Besides differing sample sizes (49 vs 135 patients), thus, statistical power, differences in selection criteria (no preselection vs selection based on cognitive symptoms), and/or timing of the intervention (semi-acute phase vs stable disease) are possible explanations for the different

findings. Another important difference with our previous RCT is that in the recent study use was made of eHealth instead of the face-to-face cognitive rehabilitation. The proven effectiveness of our face-to-face program implies that certain ingredients of the program can lead to improvements in cognitive functioning in brain tumor patients. Potentially, the eHealth intervention could be further optimized, to achieve beneficial effects for brain tumor patients. For example, maybe the program can be offered with more support of a professional, moving towards a more blended care approach. Furthermore, research generally focuses primarily on groups, whereas in clinical practice, a more patient-centered approach is used, taking into account individual differences and preferences. For example, in our cognitive rehabilitation studies, the intervention started three months after surgery. From patients' feedback it became clear that this was too early for some and too late for a few. Based on our findings with respect to the recruitment of patients, we would suggest a later timing of the intervention for future research, when patients have recovered from surgery and have resumed their daily activities. In this way, larger samples may be recruited allowing for firmer conclusions with respect to effectiveness of the intervention. When the cognitive rehabilitation program would be used in clinical care, the timing of the intervention could be adjusted to the needs of patients. Still, it is important to realize that eHealth interventions do not suit everyone, and that (referral to) psychological interventions are in line with the needs of individual patients.

### OPPORTUNITIES AND CHALLENGES OF EHEALTH

Globally, there is a large shortage of healthcare personnel.<sup>16</sup> Due to, amongst others, the aging population, the shortage of health care workers is likely to grow. Efficient use of eHealth technologies may offer a partial solution to this problem. It can increase the accessibility of interventions to patients and enables patients to follow an intervention in their own environment. In recent decades, many eHealth-apps have been developed, however, only a small proportion have been evidence-based or scientifically researched. In addition, eHealth programs are often not yet embedded in clinical care and/or reimbursed by health care insurers, which reduces accessibility to these programs for patients. Currently, the Dutch government strongly encourages the use of eHealth in health care and will provide financial support for this in the coming years.<sup>17</sup>

One of the concerns of eHealth is ensuring adherence to eHealth programs. While increasing accessibility of psychological interventions, low adherence can be a significant problem, through limited exposure to the whole program/not receiving the "full dosage".<sup>18</sup> Fortunately, adherence in our RCT was sufficient and was higher compared to adherence rates of our pilot study, with average completion of 86% of the compensation training and

91% of the retraining. There is a lack of agreement on how best to measure adherence, with the number of logins and the number of completed modules as most commonly used methods. In a review of psychological eHealth interventions, module completion (which we also used in our intervention studies as a measure of adherence) was significantly correlated with psychological outcomes.<sup>19</sup> However, due to the relatively small sample size of our intervention group ( $n = 23$ ), adherence could not be taken into account. In larger trials, it is recommended to do so, for example by looking at dose-response relationships.

In recent years, privacy protection has received much attention within healthcare. International and national laws have been further tightened, for example with the introduction of the General Data Protection Regulation (*“Algemene Verordening Gegevensbescherming”*) in May 2018. To properly protect the privacy of patients in research, there are understandably strict requirements. Within the current research project, however, this has led to several restrictions, which, moreover, were not always advantageous for patients. One example was that patients and informal caregivers were not allowed to use their own email addresses in the remind app, which hindered sending emails from the program. Also, data could not be sent to a database at the university because of stricter regulations. As a result, we as researchers did not have access to certain data (e.g., answers given by patients, number of logins and performance on the retraining game) and also, could not provide remote real-time supervision. Of course, privacy protection is very important, but one has to be careful that it does not stand in the way of development and conducting proper research in health care.

## METHODOLOGICAL CONSIDERATIONS

First and foremost, the sample sizes of some of the studies included in this dissertation were relatively small, which has led to reduced power and limitations in the statistical analyses. Recruitment difficulties were present: many patients were not eligible (according to the in-/exclusion criteria) and additionally, a substantial part of eligible patients declined participation. Declining participation is a known issue in oncological studies.<sup>20</sup> Also, studies into the use of support services demonstrated that many brain tumor patients tend not to use support services, despite unmet needs.<sup>21</sup> Examples of reasons given by patients are that they were doing well compared to other brain tumor patients or that they had prioritized other issues over their supportive care needs.<sup>21</sup> Furthermore, participants in our studies were often highly educated. It is therefore possible that participation bias had been present, potentially comprising generalizability of the results.<sup>20</sup> Taken together, future studies should take potential recruitment difficulties into account. For example, longer inclusion periods can be incorporated, and multiple participating centers can be involved in an early stage.



In our studies, use was made of the computerized neuropsychological test battery CNS VS to measure different aspect of patients' cognitive functioning and a few limitations related to the CNS VS should be mentioned. First, a test of free memory recall is not included in the CNS VS test battery. In the verbal memory test and visual memory test of CNS VS patients were asked to remember 15 words and figures respectively (randomly selected from a larger database of stimuli) and afterwards, they had to pick the 15 (to be) remembered words/figures from a list of 30. Clearly, this involves recognition in response to a cue rather than recall of information actively retrieved from one's memory without a cue. This makes the tasks easier and also, problems in memory retrieval are being overlooked. Furthermore, CNS VS does not cover all cognitive domains, for example, language, visuo-spatial function and social cognition are not assessed. Despite the limitations, CNS VS proved to be time-efficient and sensitive in the detection of (mild) cognitive deficits and change in cognitive function in patients with brain tumors.<sup>3,22</sup> Also, we established comprehensive Dutch normative data<sup>23</sup>, and developed formulae for the determination of reliable change in individuals (chapter 2) which makes the battery very suitable for repeated testing in our patient samples. Alternatively, future studies may consider the use of tests recommended by the International Cancer and Cognition Task Force (i.e. Hopkins Verbal Learning Test, Controlled Oral Word Association, Trial Making Test A/B).<sup>24</sup> If those recommended tests are used, studies can be compared more easily.

In our research, we did not assess sleep-and-wake disturbances among brain tumor patients, although these problems often co-exist and interact with symptoms of fatigue, depression and cognitive deficits.<sup>25</sup> Also, personality traits and coping style were not assessed, but may be important predictors of cognitive concerns and fatigue. Additionally, over the past years, researchers found a link between multiple molecular makers and cognitive functioning<sup>26</sup> and in the future, this link could be further explored. Ultimately, knowledge from genetic profiling might be used to identify patients who are most vulnerable for cognitive decline at an early stage. It is important to mention that a large number of studies in brain tumor patients (including chapter 2 and 3 of this dissertation) looked into associations between, amongst others, tumor characteristics, treatment modalities, epilepsy, psychological distress, fatigue, and cognitive functioning. Although in this way, new knowledge is acquired, predictions or causal relationships cannot be established. More experimental and prospective longitudinal studies are needed in the field of neuro-oncology, based on hypothesis-driven research, in addition to descriptive studies.

## FUTURE RESEARCH DIRECTIONS

As described before, novel assessment techniques could also be further explored in future studies in brain tumor patients, to obtain a more complete picture of patients everyday cognitive functioning. For example, using an Experience Sampling Method (ESM)<sup>27,28</sup> to measure cognitive functioning at multiple times throughout the day, may provide a more realistic picture of patients' daily functioning, since real-time measurement of cognitive functioning is actually integrated in the daily lives of patients. In addition, virtual environments (VE) are increasingly being used to enhance neuropsychological testing, so that they better reflect situations patients face in the outside world.<sup>29,30</sup> Furthermore, linking information from multiple modalities, including for example neuropsychological tests, imaging outcomes and immunological parameters<sup>31</sup>, may also provide new insights into the multifactorial determinants of cognitive dysfunction in brain tumor patients and may reveal potential targets for treatment.

Compared to the number of studies on incidence, severity and correlates of cognitive deficits in brain tumor patients, little research has been conducted on different treatment options for these deficits. Besides cognitive rehabilitation studies, the effects of pharmacological treatments and exercise programs have been explored in brain tumor patients in the past decades. Donepezil, armodafinil and modafinil are the most studied pharmacological agents with respect to cognitive functioning in brain tumor patients. Findings on the effects of those agents on cognitive functioning are mixed, but the most evidence for benefits has been found for donepezil.<sup>14</sup> However, long-term follow-up assessments are lacking in almost all studies on the effects of pharmacological agents on cognitive performance. Furthermore, not many exercise intervention studies have been carried out in patients with brain tumors (yet). The few studies that were conducted demonstrated feasibility of exercise interventions for brain tumor patients and suggest (small) positive effects on cognitive functioning and wellbeing.<sup>32,33</sup> It would be interesting to study the combination of physical exercise and cognitive rehabilitation in brain tumor patients, since this combination has yielded positive results in other populations.<sup>34-36</sup> Lastly, the overlap in symptoms of depression, anxiety, fatigue, insomnia and cognitive concerns can be used in advance. For instance, interventions that address emotional problems, can potentially have an indirect positive effect on cognitive functioning. Taken together, the field of interventions for cognitive deficits in brain tumor patients is developing, but still, a lot of work needs to be done in the future.

Besides interventions aimed at improving cognitive functioning during or after medical treatment, increased attention has been paid to cognition-sparing medical treatment strategies for brain tumor patients. Examples of cognitive-sparing techniques include awake

brain tumor surgery, stereotactic radiotherapy, proton therapy and hippocampal sparing during radiotherapy.<sup>36</sup> The findings on these techniques seem promising so far, but further research (especially on long-term effects of those techniques) is needed to draw clear conclusions, in order to facilitate transfer of innovative techniques into clinical practice.

### IMPLICATIONS FOR CLINICAL PRACTICE

In this dissertation, the need for routine neuropsychological assessment has been emphasized, amongst others, to be able to inform patients properly before surgery about possible cognitive outcomes, and to provide appropriate care timely. It should be noted that with repeated measurement in individuals in clinical practice, it is important to take into account practice effects and imperfect test-retest reliability, to enable proper interpretation of scores. In addition to cognitive function, symptoms of fatigue should be monitored during the disease trajectory, since this is a common and severe and persistent symptom among brain tumor patients. Cognitive symptoms or fatigue can also manifest or aggravate at a later stage, and therefore, long-term follow up after surgical resection is recommended.

Neuropsychological results of patients can be discussed in multidisciplinary consultations, facilitating timely signaling and well-considered referral to, amongst others, rehabilitation services or psychological care. Intervention studies make use of strict protocols, in order to be able to demonstrate potential beneficial effects of the intervention. In clinical practice, interventions can be more tailored to the needs and situations of patients and family members. For example, timing of the intervention can be adapted to patients' needs and treatment goals can be set in collaboration. Psychoeducation on cognitive functioning (as incorporated in the *ReMind*-app) can be helpful for some brain tumor patients. However, more research has to be done on cognitive rehabilitation in larger samples of brain tumor patients, to be able to draw firm conclusions about possible effects of cognitive rehabilitation.

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## APPENDICES

Nederlandse samenvatting

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Dankwoord







## NEDERLANDSE SAMENVATTING | DUTCH SUMMARY

### Achtergrond

Patiënten met een hersentumor worden vaak geconfronteerd met cognitieve stoornissen, vermoeidheid en psychische klachten ten gevolge van de ziekte en de behandeling. Deze symptomen kunnen het dagelijks leven van patiënten, en dat van hun naasten, ten negatieve beïnvloeden en uiteindelijk zorgen voor een lagere kwaliteit van leven. In de afgelopen jaren is er binnen de neuro-oncologie meer aandacht gekomen voor deze cognitieve en psychologische uitkomstmaten, naast medisch-oncologische uitkomstmaten zoals overleving en tumorprogressie. Hoewel er nu steeds meer bekend is over de prevalentie en ernst van cognitieve stoornissen bij hersentumorpatiënten, is er veel minder onderzoek gedaan naar mogelijke behandelingen voor deze stoornissen. In dit proefschrift wordt er verder gekeken naar het meten van neuropsychologische uitkomsten bij hersentumorpatiënten, en daarnaast ook naar het inzetten van postoperatieve cognitieve revalidatie, met als uiteindelijk doel de nazorg voor patiënten die geopereerd worden aan een hersentumor te kunnen verbeteren.

### Belangrijkste bevindingen

In het eerste deel van het proefschrift zijn verschillende aspecten van het meten van cognitieve functies en vermoeidheid bij hersentumorpatiënten onderzocht. In het tweede gedeelte werd er gefocust op de haalbaarheid en effectiviteit van cognitieve revalidatie via de *ReMind*-app.

In **hoofdstuk 2**, werden de test-hertest betrouwbaarheid en mogelijke oefeneffecten van de gecomputeriseerde neuropsychologische testbatterij CNS Vital Signs geëvalueerd, binnen een steekproef van Nederlandse gezonde volwassenen. Er werden 158 participanten geïncludeerd, en bij de 3-maanden en 12-maanden vervolgmetingen, werden er respectievelijk 131 en 77 participanten opnieuw getest. Test-hertest correlatiecoëfficiënten varieerden sterk tussen de cognitieve domeinen van de testbatterij (ICCs tussen de 0.40 en 0.88). Wat betreft oefeneffecten, zagen we dat participanten op de tweede meting (3 maanden later) significant beter scoorden op de Stroop Test, Symbool Coderen en op de Shifting Attention Test, wat leidde tot significant hogere scores op de domeinen Cognitieve Flexibiliteit, Verwerkingssnelheid en Reactietijd. Er werden geen significante veranderingen in prestatie gevonden tussen de tweede en de derde meting. Er werden formules opgesteld (RCIs), waarbij test-hertest betrouwbaarheid en oefeneffecten in acht werden genomen, om individuele verandering in cognitieve prestaties op de CNS VS beter te kunnen interpreteren bij gebruik van de batterij in onderzoek en in de klinische praktijk.

In **hoofdstuk 3**, werd het executief functioneren van hersentumorpatiënten nader onderzocht, waarbij er gebruik werd gemaakt van zelfrapportage vragenlijsten, informant vragenlijsten en testen voor het executief functioneren. Overeenstemming tussen patiënt en naaste, wat betreft het executief functioneren van de patiënt, werd onderzocht in 47 paren. Patiënten rapporteerden significant meer problemen op de Metacognitie index van de BRIEF-A in vergelijking met normen, maar ook in vergelijking met hun naasten. Over het algemeen was de overeenstemming tussen patiënt en naaste voldoende. Scores op vragenlijsten bleken nauwelijks samen te hangen met scores op de executieve testen. Vervolgonderzoek zou zich kunnen richten op de mismatch tussen zelfrapportage en testprestaties. Tevens zouden nieuwe manieren van meten (bijvoorbeeld m.b.v. virtual reality) voor het in kaart brengen van alledaags executief functioneren verder onderzocht kunnen worden voor hersentumor patiënten.

In **hoofdstuk 4**, werd de prevalentie, de ernst en mogelijke correlaten van vermoeidheid in meningeoompatiënten (WHO-graad I) onderzocht, met behulp van een gevalideerde multidimensionele vragenlijst (de MVI). Zowel voor operatie ( $n = 65$ ) als één jaar na operatie ( $n = 53$ ) scoorden meningeoom patiënten significant hoger op alle schalen van de MVI in vergelijking met normatieve gegevens. In een subgroep van patiënten die beide meetmomenten ondergaan hadden ( $n = 34$ ) zagen we dat de gemiddelde scores niet veranderden over tijd op de schalen Algehele Vermoeidheid, Fysieke Vermoeidheid en Mentale Vermoeidheid. Verbeteringen werden geobserveerd op de schalen Verminderde Motivatie en Verminderde Activiteit. Patiënten rapporteerden dus dat zij een jaar na operatie gemotiveerder en actiever waren, maar nog steeds vermoeidheid ervaarden. Op individueel niveau zagen we dat 68% van de patiënten verhoogd scoorden op één of meer schalen van de MVI voor operatie, en postoperatief was dit percentage 57%. Vermoeidheid was geassocieerd met zelf-gerapporteerde cognitieve klachten, angst- en depressie symptomen. Vanuit dit onderzoek werd het duidelijk dat vermoeidheid een erge, veelvoorkomende en persisterende klacht is in patiënten met een meningeoom die hieraan geopereerd worden, en dat het meer aandacht verdient van zowel onderzoekers als clinici binnen de neuro-oncologie.

In het tweede gedeelte van het proefschrift werd er gekeken naar de haalbaarheid en effectiviteit van het cognitieve revalidatieprogramma *ReMind*. De iPad-app *ReMind* is gebaseerd op het eerder effectief gebleken face-to-face cognitief revalidatieprogramma van onze onderzoeksgroep. Het programma bestaat uit psychoeducatie, compensatietraining en aandachts-training. In **hoofdstuk 5** zijn de resultaten van het pilotonderzoek beschreven. Hierin werden de haalbaarheid van- en mogelijke barrières voor het gebruik van de cognitieve revalidatie-app geëvalueerd binnen een klinische setting bij 15 patiënten

met een meningeoom of laaggradig glioom. Het rekruteren van voldoende participanten bleek moeilijk: een aanzienlijk deel van de patiënten die gepland stonden voor operatie kwamen op voorhand al niet in aanmerking voor het onderzoek (zij voldeden niet aan de inclusiecriteria) en van de patiënten die wél uitgenodigd werden, weigerde ongeveer de helft om deel te nemen aan het onderzoek. De deelnemers volbrachten gemiddeld 71% van de compensatietraining en 76% van de aandachts-training. Over het algemeen werd het programma goed beoordeeld door de patiënten. Zij gaven aan dat een iPad-app een goede manier was om het cognitieve revalidatieprogramma te volgen. Sommigen vonden de oefeningen van de aandachts-training te makkelijk, waardoor we deze na de pilotstudie uitgebreid hebben met moeilijkere oefeningen.

Na de pilotstudie startte er een gerandomiseerd studie (RCT), om de mogelijke effecten van het cognitief revalidatieprogramma op cognitieve prestaties en patiënt-gerapporteerde uitkomstmaten te evalueren. Het onderzoeksprotocol van de RCT werd uitgebreid beschreven in **hoofdstuk 6**. Het doel was om preoperatief 150 patiënten met een meningeoom of laaggradig glioom te includeren. Met een uitvalpercentage van 33%, zouden we verwachten om 100 patiënten op te volgen (50 in de interventiegroep en 50 in de controlegroep). Neuropsychologische screening werd uitgevoerd voor operatie (T0) en drie maanden na operatie (T3). Op T3 werden patiënten toegewezen aan de interventiegroep of controlegroep. Patiënten in de interventiegroep volgde het cognitief-revalidatieprogramma voor 10 weken. Zes maanden (T6) en één jaar (T12) na operatie werden vervolg neuropsychologische metingen verricht.

In **hoofdstuk 7** werden de resultaten van de RCT gepresenteerd. Net als in de pilotstudie verliep het rekruteren van patiënten moeizaam, waardoor er uiteindelijk een relatief kleine steekproef over bleef voor de analyses (interventie groep  $n = 23$ , controles  $n = 26$  op T6). Therapietrouw was hoger in de RCT dan in de pilotstudie, waarbij gemiddeld 86% van de compensatietraining was afgerond en 91% van de aandachts-training. Daarentegen vielen er meer patiënten uit het onderzoek in de RCT dan in de pilotstudie. De *ReMind*-app werd opnieuw positief beoordeeld door de patiënten. Er werden geen significante verschillen gevonden tussen interventiegroep en controlegroep in groepsgemiddelden of RCI's van cognitieve prestaties en patiënt-gerapporteerde uitkomstmaten. Het percentage patiënten met cognitieve stoornissen was vergelijkbaar tussen de groepen op T3 en T6 ( $\pm 70\%$ ), echter een jaar na operatie zagen we dat 35% van de patiënten in de interventiegroep afwijkende scores vertoonde versus 68% in de controlegroep, wat een significant verschil was. Voor vervolgstudies naar (eHealth) cognitieve revalidatieprogramma's, zou een latere timing van de interventie in overweging kunnen worden genomen (bijvoorbeeld in een fase waarbij de ziekte stabiel is), gebaseerd op onze bevindingen m.b.t. het includeren van patiënten.

## Conclusies en aanbevelingen

In deze dissertatie werd het belang van routinematig neuropsychologisch screenen benadrukt, enerzijds om patiënten voor operatie beter te kunnen informeren over mogelijke cognitieve uitkomsten na operatie, en daarbij om passende zorg tijdig in te kunnen zetten. Bij herhaaldelijke neuropsychologische testafnames is het van belang om oefeneffecten en matige test-hertest betrouwbaarheid van instrumenten in acht te nemen, om de individuele testcores van patiënten accuraat te kunnen interpreteren. Naast cognitieve symptomen, is het belangrijk om symptomen van vermoeidheid te monitoren tijdens het ziekteproces, aangezien dit een veelvoorkomend en persisterend symptoom blijkt te zijn bij hersentumorkpatiënten. Cognitieve stoornissen en vermoeidheid kunnen verergeren over de tijd of pas later in het ziekteproces ontstaan. Om die reden is het noodzakelijk om patiënten lang genoeg op te volgen na een neurochirurgische ingreep.

Resultaten van de neuropsychologische testen en vragenlijsten kunnen meegenomen worden in multidisciplinair overleg, om vroeg-signalering en weloverwogen tijdige verwijzing naar bijvoorbeeld revalidatie of psychologische behandeling te bespoedigen. Bij interventiestudies wordt er gebruik gemaakt van strikte protocollen, om eventuele positieve effecten te kunnen meten. In de klinische praktijk daarentegen, kunnen interventies veel meer afgestemd worden op de behoeften en situaties van patiënten en hun naasten. De timing van de interventie kan onder andere aangepast worden aan hun behoeften en doelen van de behandeling kunnen in samenspraak bepaald worden. Psychoeducatie over cognitief functioneren (zoals opgenomen in de *ReMind*-app) kan helpend zijn voor patiënten met een hersentumor. Er is echter nog veel meer onderzoek nodig op het gebied van cognitieve revalidatie in deze patiëntpopulatie, met grotere steekproeven, om duidelijke conclusies te kunnen trekken over de mogelijke effecten van cognitieve revalidatie.





## ABOUT THE AUTHOR

Sophie van der Linden was born on May 28, 1990 in Bergen op Zoom, the Netherlands. After completing secondary school at Gymnasium Juvenaat, she moved to Leiden to study psychology. At Leiden University, she completed the bachelor program in 2.5 years. Subsequently, she studied Medical Psychology and obtained her master's degree cum laude at Tilburg University in 2013. Afterwards, she held jobs as a psychologist and research assistant. In 2015, she started her PhD program at the Department of Neurosurgery of the Elisabeth-TweeSteden Hospital Tilburg, in collaboration with the Department of Cognitive Neuropsychology of Tilburg University, focusing on cognitive functioning and cognitive rehabilitation in patients with primary brain tumors. During the third year of her PhD research, she started to combine her PhD research with a part-time position as a psychologist in geriatric rehabilitation care of De Wever in Tilburg. In January 2020, she will start with a two-year training to obtain her postmaster degree as a health care psychologist at De Wever. In the future, she hopes to combine working as a psychologist in clinical practice with conducting research. This, with the ultimate goal of being able to contribute to narrowing the gap between research and practice.



*'Sophie op een brug'*  
By Xaf van der Linden





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Sophie

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A stylized, handwritten signature in black ink, consisting of a large, flowing 'S' followed by a smaller, more delicate flourish.



